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CELL TYPES IN THE GLIOMAS

THEIR RELATIONSHIP TO NORMAL NEUROHISTOGENESIS *

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LOS ANGELES

Tumors of the brain substance, commonly known as gliomas, have offered a fascinating field of study since they came to be recognized as a pathologic entity. Classed at first with "cancers" and sarcomas as a whole, they tended later to be segregated into a group by themselves, based on the idea that they had a peculiar origin from the brain tissue. Without the aid that the microscope could give as to the nature of their constituent tissues, pathologists of the early decades of the nineteenth century designated them as encephalomas or cerebromas. These names were short lived, however, for after his earlier histologic studies on the neuroglia, Virchow came to associate this group of tumors with the supporting tissues of the nervous system and called them gliomas. His classic descriptions of the gross appearance of the various types of gliomas remain unsurpassed, although many of his conceptions as to the character of their cellular elements must be disregarded. In spite of recent advances in knowledge regarding their structure and growth characteristics, the problem of their histogenic processes has not been entirely solved. In the hope of contributing in a small way to the study of the problem, this investigation was undertaken.

It soon became obvious that the problem presented two distinct features: (1) a study of the morphologic aspects of the cells composing the various tumors and (2) the determination of the essential nature of these elements and their relationship to the stages of normal neurohistogenesis. The first phase of the problem has been more or less completely investigated even by the pioneers in the field, who described and illustrated the occurrence of apolar, unipolar, bipolar and multipolar

* Submitted for publication, April 12, 1930.

* From the Neurosurgical Service of Dr. Carl W. Rand, Los Angeles County General Hospital.

1. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1864-1865, vol. 2, pp. 125-151.

2. Klebs, E.: Beiträge zur Geschwülstelehre: II. Die Geschwülste des nervösen Centralapparates, Vrtljsschr. f. prakt. Heilk. **133**:1, 1877.

3. Osler, William: Structure of Certain Gliomas, Philadelphia M. News, Feb. 20, 1886; quoted by Mills and Lloyd, in Pepper: System of Medicine, Philadelphia, Lea Brothers & Company, 1886, vol. 5, p. 1047.

tumor cells. Virchow,[1] Klebs,[2] Osler,[3] Bramwell[4] and Stroebe[5] considered these various forms in detail, so that there is little to be added by way of description.

The second cytologic feature includes the proper interpretation of these various cell forms. This portion of the field is by no means unexplored, for Bailey and Cushing, by the use of the specific metallic methods, laid a broad foundation for future investigation in their recent epoch-making contribution. They attempted to associate the cellular elements of a given glioma with a stage in the normal histogenic process. This presents a difficulty, because, as these authors fully realized,[6] each tumor contains not one, but often several different types of cells. If a plan could be devised in which a certain degree of latitude could be allowed for the histogenic process as it occurs within the growing tumor itself, a nearer approach to the solution of the problem may be made.

Furthermore, the question not only of their development but also of their possible origin is less complex if one notes the normal histogenic process as it occurs in the brain rather than in the cord. The essential differences in cellular development in the pallium as contrasted with that in the embryonic cord may be considered under three headings: (1) the greater migratory activity of the developing cells, (2) the more complex morphology of the gross structures and (3) the elaboration of intricate commissural, association and projection systems. A prolonged discussion of pallial development is not in order in this connection, and it will suffice to say that undifferentiated cells are to be found as late as the third and fourth months of fetal life well out in the looser tissues of the mantle layer. These bipotential cells are undoubtedly the origin of many of the glial and ganglionic elements of the cortical and subcortical regions of the adult brain. It is possible that such indifferent elements may be isolated from their normal paths by the development of the corpus callosum, the fibers of which are already beginning to intersect the paths of such corticifugally coursing elements.

MATERIAL AND METHODS

In order to study the cell types of the gliomas, specimens of fifty tumors were collected, with the available clinical records. A large proportion of the material was contributed by the resident pathologists of the Los Angeles County General Hospital, the remaining portion,

4. Bramwell, Byrom: Intracranial Tumours, Philadelphia, J. B. Lippincott Company, 1888, pp. 17 and 222.

5. Stroebe, H.: Ueber Entstehung und Bau der Hirngliome, Beitr. z. path. Anat. u. z. allg. Path. **18**:405, 1895.

6. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926, pp. 53, 54, 101 and 102.

in great part, by the pathologists of the laboratories of the College of Medical Evangelists and of the Good Samaritan, Children's, White Memorial and Pasadena Hospitals. A few specimens were given to me by physicians in private practice.

In addition to the routine methods, I utilized the following staining and impregnation processes: Mallory's phosphotungstic acid-hematoxylin and aniline blue methods; Cajal's gold sublimate and reduced silver (the latter being used to demonstrate neuroblasts), and Hortega's silver carbonate and fourth variant methods. Penfield's combined method for the study of oligodendroglia and microglia in formaldehyde-fixed tissues was also used.

Early in the course of this investigation it was realized that a complete report of the study could not be included in this paper. I have therefore limited myself here to a general survey of the field in a brief consideration of the various types of gliomas. More specific studies have been made the subject of further contributions, which will be forthcoming.

FUNDAMENTAL CONCEPTIONS

It is evident that two factors largely influence the histologic architecture and composition of a given glioma: (1) the rate and degree of differentiation of its constituent elements and (2) the stage and apparent situation of the parent cells at the moment of the assumption of neoplastic activities. Many of the developmental stages can be morphologically and specifically demonstrated within the tissues of a single tumor, so that a more or less complete review of the normal process is presented. Furthermore, the extent of the process varies greatly in the individual tumors of a given group. The tissue architecture is influenced largely by the tendency of its cells to assume primitive arrangements or altered by accompanying degenerative changes. Such primitive tendencies are manifested by the formation of cell rings ("annulation forms" of Tooth) or pseudorosets of various types. In a few rare tumors, the grouping of the cells suggests the arrangement found in the neural tube in the early period of embryonal life.

It seems fairly clearly demonstrated also that in the embryonal gliomas the earliest and most primitive type of cell is a round or oval form with a mere ring of cytoplasm about a chromatin-rich nucleus. The cells of this type are much alike in the various members of the group, and in many of the medulloblastomas and neuroglioblastomas they compose the greater mass of the tissue. This cell seems to be a counterpart of the indifferent cell of the developing pallium, having bipotentialities as far as the proliferation of glioblasts and neuroblasts

are concerned. This seems to be proved by the fact that preparations by specific methods demonstrate neuroblasts, as well as glioblasts.

The mode of cell division in the various tumors is interesting and sheds some light on their biologic activities. In a general way, it is evident that in the more embryonal forms, cell division takes place largely by mitosis. In the less malignant individuals of the neuroglioblastomas, the astroblastomas and the gangliogliomas, there are marked evidences of amitotic division as manifested by tumor giant cells and indented and constricted nuclei. In the astrocytomas, cell division takes place entirely by this method. From this standpoint, the type of cell division gives a rough estimate as to the degree of malignancy of the tumor in question.

A SUGGESTED CLASSIFICATION OF THE GLIOMAS

With these fundamental characteristics of gliomas in mind, the following classification is suggested, based necessarily on the concept that the tumors of this group have their origin in embryonal cell "rests".[7]

Group 1.—Gliomas the cellular arrangement of which to a greater or less degree is suggestive of that of the primitive neuro-epithelium. In some instances, it is probable that some of the cells are capable of differentiating into neuroblasts and glioblasts.

Group 2.—Gliomas arising from embryonic or adult ependymal tissue, growing into the ventricular system instead of the brain substance.

Group 3.—Gliomas apparently arising from cells that have migrated from the environs of the neural cavity. The mother cell of such gliomas resembles the migrating undifferentiated cells of the pallium and like them is bipotential, capable of forming glioblasts or neuroblasts. The malignancy of the various types depends on the degree of cellular differentiation.

Group 4.—Gliomas that develop in consequence of the division of fully developed cells, usually of glial type. Fully matured ganglion cells are probably not capable of neoplastic proliferation.

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7. It must be admitted that while, in many respects, Cohnheim's theory of the origin of tumors as applied to those arising from brain substance, seems almost conclusive, it lacks much of being definitely proved. Most of the investigators on the subject, particularly the Germans, stress its importance, and according to Bielschowsky, it is indispensable in explaining the origin of the gliomas. Their association with congenital malformations of the brain, with malformations of the viscera and the extremities and with atypical development (status thymicus), as well as their occasional multiplicity, are strong arguments in favor of this conception.

Group 5.—Tumors arising from the appendages of the brain, the pineal and the pituitary glands.[8]

Group 1.—It has not been my good fortune to find a case of the kind of gliomas included in group 1. They are rare, and for their essential characteristics I am dependent on reports of cases in the literature. Such tumors have a greater or less tendency to form primitive arrangements of their constituent cells. Bailey and Cushing included them in the terms of medullo-epithelioma and neuro-epithelioma.

The medullo-epithelioma is evidently a tumor composed of reduplications of bandlike masses of cells that suggest the medullary tube in the early days of embryonic life. These cells may be anticipated as being too immature to be classified in most instances, but it is possible that some of them might have differentiated later into stages suggestive of glioblasts or neuroblasts. These tumors are usually malignant, and mitoses are numerous; hence it is unlikely that the cells progress far in the histogenic process.

The second type, the neuro-epithelioma, presents a somewhat different picture. While in some instances the cells may be arranged in layers about cavities of various sizes, the tendency is to form rosets of what are evidently primitive ependymal cells, as cilia have been demonstrated in some instances. In reporting a case of this type, Ribbert[9] mentioned the occurrence of both glioblasts and neuroblasts and suggested the name of spongioneuroblastoma for it. If his observations were correct, this tumor presents some tendency to differentiate into the various essential constituents of embryonal nervous tissue. Bucy and Muncie[10] reported the presence of cells impregnated by the reduced silver method, but since they considered the method as utilized to be nonspecific, they attached no significance to the observation. With Bailey and Cushing, I am inclined to believe that this tumor is less primitive than the medullo-epithelioma, and further that it is capable of some degree of differentiation into glial and ganglionic daughter elements.

Group 2.—Tumors of this group, arising from embryonal or adult ependymal cells, grow internally into the canal system rather than externally into the brain substance. They show no tendency to differentiate into cells other than of their own type. In specific preparations

8. The word "pituitary" is here used advisedly, as tumors of the posterior lobe, the only portion of the organ of neural origin, are practically unheard of. The adenomas and carcinomas of the pars anterior and the congenital cysts arising from the remains of the craniopharyngeal canal are not true tumors of the brain.

9. Ribbert, H.: Ueber das Spongioblastom und das Gliom, Virchows Arch. f. path. Anat. **225**:195, 1918.

10. Bucy, P. C., and Muncie, W. C.: Neuroepithelioma of the Cerebellum, Am. J. Path. **5**:157, 1929.

of typical ependymal gliomas (ependymoblastomas), I found nothing suggestive of glioblasts or neuroblasts. Bailey[11] originally divided ependymal gliomas into ependymoblastomas and ependymomas, but the tendency of others is to group them all under ependymomas.[12] Roussy, Lhermitte and Cornil included them under the term of ependymogliomas.[13]

It is reasonable to include tumors growing from the choroid plexus in this group, as the mother tissue is modified ependyma. Recent studies have elaborated the details of this rather interesting but rare form of intracranial tumor.[14]

Group 3.—Tumors of this group consist essentially of round or oval indifferent cells the progenitors of which have become separated in a variable degree from the neural cavity. If they show any tendency to differentiate, owing to a slower rate of growth, embryonal forms of glioblasts and neuroblasts are frequently found. The various members of the group will be considered separately.

The medulloblastoma, introduced as a distinct entity by Bailey and Cushing,[15] is a tumor that characteristically arises from the roof of the fourth ventricle. It likely has its beginnings in the indifferent cells of the anterior medullary velum found in a large percentage of normal brains. It seems evident that the primary cell is round or oval and is fairly uniform in size and shape. Its daughter cells, medulloblasts, develop tails, which are not impregnated for the most part by the specific methods. A few cells seem to evidence their bipotentialities by developing into glioblasts or neuroblasts. Bailey and Cushing observed that the spinal metastases are composed of the small round or oval cells, which is further evidence that they are the primary and hence more malignant form of cell. In one of my cases, I found pseudorosets that resembled those of the ependymoblastomas and that may have been due to an inclusion of ependymal "rests" in a developing

11. Bailey, Percival: A Study of Tumors Arising from Ependymal Cells, Arch. Neurol. & Psychiat. **11**:1, 1924.

12. Penfield, Wilder: Principles of the Pathology of Neurosurgery, Nelson's Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 2, pp. 329 and 333.

13. Roussy, G.; Lhermitte, J., and Cornil, L.: Essai de classification des tumeurs cérébrales, Ann. d'anat. path. **1**:333, 1924.

14. Davis, L. E., and Cushing, H.: Papillomas of the Choroid Plexus, with a Report of Six Cases, Arch. Neurol. & Psychiat. **13**:681, 1925. Van Wagenen, W. P.: Papillomas of the Choroid Plexus: Report of Two Cases, One with Removal of Tumor at Operation and One with "Seeding" of Tumor in the Ventricular System, Arch. Surg. **20**:199, 1930.

15. Bailey, P., and Cushing, H.: Medulloblastoma Cerebelli: A Common Type of Midcerebellar Glioma of Childhood, Arch. Neurol. & Psychiat. **14**:192, 1925. 1925.

medulloblastoma.[16] This group of tumors is to be made the subject of further study.

The tumor long known as the gliosarcoma and more recently as spongioblastoma multiforme[17] or glioblastoma multiforme[18] I have come to call neuroglioblastoma because in most of the twenty-eight cases of this type that I have studied, I have been able to find neuroblasts, as well as glioblasts. While this fact has not been considered by recent writers, many of the earlier observers had in mind the possibility that embryonic forms of nerve cells occurred in the various gliomas.[19] Not unlike the medulloblastoma, it has for its essential cell an apolar bipotential cell, which in some cases constitutes the greater mass of the constituent elements. In the slower growing tumors, apolar, unipolar and bipolar (and occasionally multipolar) glioblasts and neuroblasts are to be found. From analogy, this type of tumor is derived from an indifferent cell that has migrated farther from the environs of the neural canal and, after lying dormant until adult life, has assumed neoplastic characteristics (according to the cell rest theory of origin). These cells may have been cut off and isolated by the developing fibers

16. It is not to be surprised at that ependymal tissue should be found occasionally in medulloblastomas, when it is realized that the roof of the fourth ventricle seems to be the common site of origin of both types of tumors. In the case referred to, it was difficult to determine what the nature of the tumor was. Its cells were largely those of medulloblastoma, some of which had differentiated into neuroblasts. It contained many pseudorosets typical of ependymoblastoma (with central blood vessel), and many of its cells contained blepharoplasts suggestive of ependymal cells.

17. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme, a Primary Malignant Form of Brain Neoplasm: Its Clinical and Anatomic Features, Arch. Neurol. & Psychiat. **14**:139 (Aug.) 1925.

18. Bailey, Percival: Further Remarks Concerning Tumors of the Glioma Group, Bull. Johns Hopkins Hosp. **40**:354, 1927. Buckley, R. C.: Tissue Culture Studies of the Glioblastoma Multiforme, Am. J. Path. **5**:467, 1929.

19. The conception that gliomas contain nervous elements is an interesting one to trace in the literature. It had its birth, apparently, in the studies of Klebs, who, wrongly interpreting the nature of the engulfed and degenerating ganglionic elements in the margins of invasive gliomas, applied the name of neurogliomas to this group of tumors. Since that time the presence of neuronic elements has been occasionally suggested but stressed little. In the drawings of Bramwell and Stroebe can be seen cells with vesicular nuclei and enclosed darkly staining nucleoli, evidently neuroblasts. Such elements were presumed to be present in neuro-epithelioma by Ribbert, and are now proved to be present in gangliogliomas (ganglioneuroma, ganglioglioneuroma). Bailey and Cushing further found them in the medulloblastomas, and my investigations seem to establish their presence in most cases of neuroglioblastoma in this series (those in which the cells tended to differentiate) and in the few cases of astroblastoma the tissues of which were suitable for study. The presence of neuronic elements in gliomas has been considered in an abstract way by Storch, Borst and Meyer and more recently by Roussy, Lhermitte and Cornil.[18]

of the corpus callosum, which the tumor so frequently involves. Its close relation to the medulloblastoma is further suggested by the occasional tendency of its cells to form pseudorosets, identical in appearance with those of the latter tumor. Tooth [20] found them in great numbers in one of his cases, and he described them under the term of "annulation forms."

The position of the astroblastoma is not entirely clear. There were but three cases in the series under consideration, and I do not feel free to draw positive conclusions. From its tendency to radiate about the blood vessels, from the presence of cells similar to those in the neuroglioblastoma, and from its less malignant characteristics, the relative position assumed for it by Bailey and Cushing seems logical. In the few cases that have come to my attention, I have been able to find local "developing nests" of neuroblasts with the reduced silver method. These cells seemed to be largely unipolar. In this sense, the astroblastoma has a similar origin in an indifferent cell which has a tendency to differentiate more completely. The tumor demands further study.

The last of the tumors in this group, commonly but incorrectly known as the ganglioneuroma, has been shown to be composed of embryonal and adult forms of both glial and ganglionic elements. The presence of both types of cell has been recognized by the German investigators for many years, and they indicate this fact by calling the tumor a "ganglioglioneuroma." In the series of gliomas under consideration, I have found three unquestioned cases and two others that seem to be a combination of it and a neuroglioblastoma multiforme. To specify the nature of the constituent cells, I have adopted the name suggested but not utilized by Ewing,[21] that of ganglioglioma. It is undoubtedly more common than usually supposed and should be thought of when a small, fairly well circumscribed glioma is encountered in the cerebral hemispheres or the floor of the third ventricle. It is likely that many of the cases described in the literature as cases of "neurinoma centrale" must be of this type (see especially those of Josephy [22] and MacPherson [23]). The studies on this tumor will appear in forthcoming contributions.[24]

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20. Tooth, H. H.: Some Observations on the Growth and Survival Period of Intracranial Tumours, Based on the Records of 500 Cases, with Special Reference to the Pathology of the Gliomas, Brain **35**:61, 1912.

21. Ewing, J., quoted by Perkins, O. C.: Ganglioglioma, Arch. Path. **2**:11, 1926.

22. Josephy, H.: Ein Fall von Parobubie und solitärem zentralem Neuriom, Ztschr. f. Neurol. u. Psychiat. **93**:62, 1924.

23. MacPherson, D. J.: Studien über den Bau und die Lokalisation der Gliom, mit besonderer Berüchsichtigung ihres Missbildungscharakters, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **27**:123, 1925.

24. Courville, C. B.: Ganglioglioma: Tumor of the Central Nervous System, Arch. Neurol. & Psychiat. **24**:439, 1930; Ganglioglioma, a Further Report, with Special Reference to Those Occurring in the Temporal Lobe, ibid., to be published.

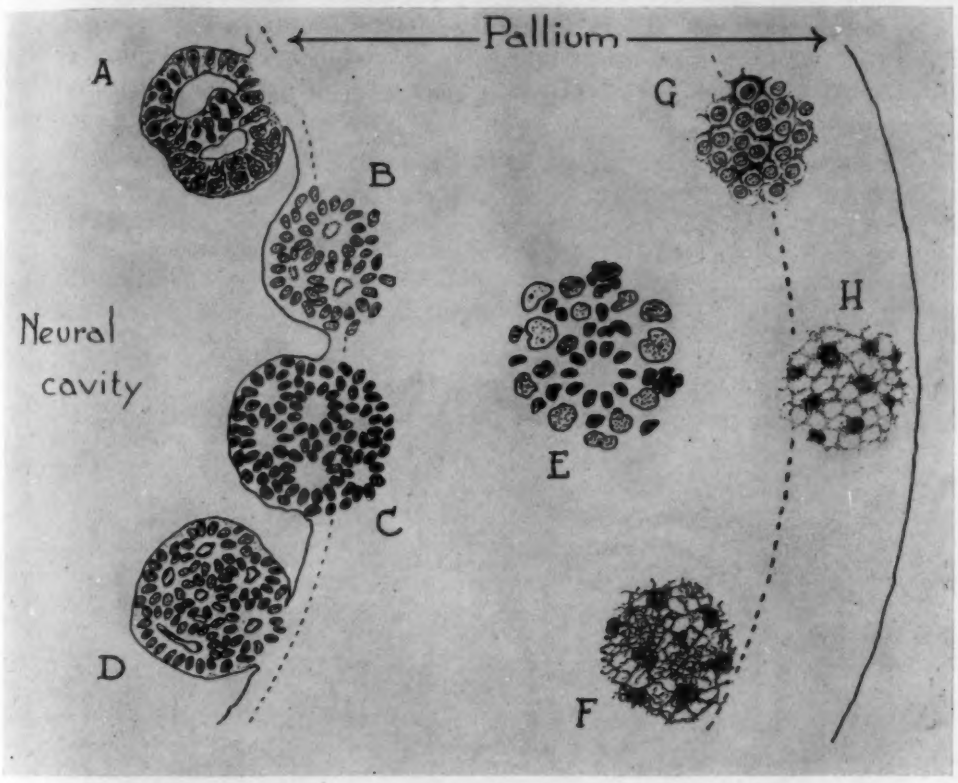

Fig. 1.—Diagrammatic schema indicating the point of development of the various gliomas as compared with the embryonal pallium. *A* is a medullo-epithelioma, which is formed of reduplications of cell layers suggesting the structure of the embryonal neural tube. They usually project into the ventricular system. *B* is a neuro-epithelioma, which usually grows into the brain substance, and its cells tend to form rosets. *C* is a medulloblastoma, which grows into the cerebellum as well as downward into the fourth ventricle. *D* is an ependymal glioma (ependymoblastoma, ependymoma), which grows into the ventricular system, its cells forming pseudorosets by grouping themselves about the blood vessels. *E* represents a group of gliomas (neuroglioblastoma, astroblastoma and ganglioglioma), which consist of developing glial and ganglionic elements. They vary in degree of differentiation and make feeble attempts to form pseudorosets. *F* is an astrocytoma protoplasmaticum, developing probably from amitotic division of adult cell forms. *G* illustrates the oligodendroglioma, which is composed of adult and possibly embryonic forms of oligodendroglia. *H* represents astrocyoma fibrillare, which is formed by amitotic division of adult fibrillary astrocytes.

The gliomas in this group, then, are composed of small round or oval cells apparently corresponding to the indifferent cells in normal neurohistogenesis. These elements have a variable tendency to differentiate into glioblasts and neuroblasts. The impression gained from a study of them is that there is a greater propensity to form glioblasts

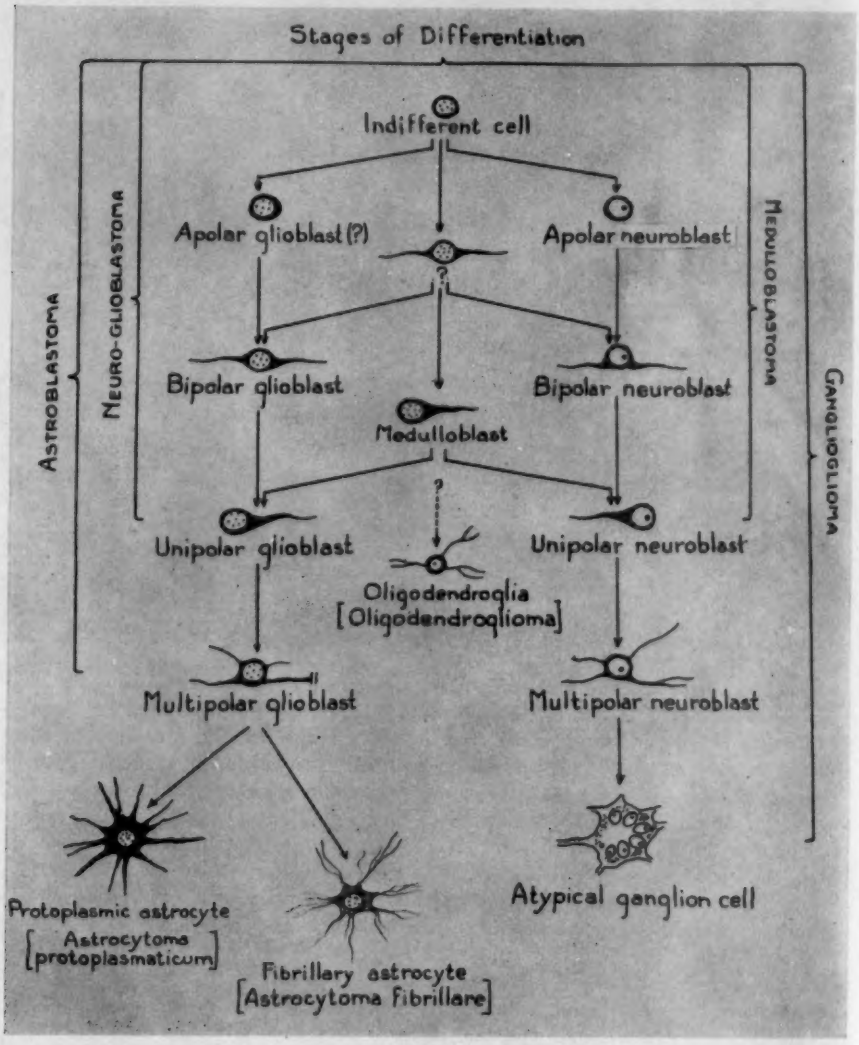

Fig. 2.—Schema indicating histogenic stages that may be demonstrated in the gliomas studied in this series. The extent of differentiation in the various tumors is indicated by brackets. The various tumors are shown to contain both developing glioblasts and neuroblasts, except those in which the name of the tumor appears below an individual cell.

than neuroblasts, the proportions found in normal nervous tissue being roughly maintained. This seems to be true even in the case of the ganglioglioma, according to the German investigators, though the greater size of the ganglionic elements make them the more conspicuous.

Group 4.—The fourth group of gliomas is composed of tumors having their origin from adult cell forms, no embryonal elements being found in their tissues. The group is composed largely of astrocytomas, which structurally are made up of adult fibrillary or protoplasmic astrocytes or both. From the descriptions given, it is likely that the tumor originally described by Bailey and Cushing and investigated further by Bailey and Bucy [25] under the term of oligodendroglioma should be included in this group, both from the adult character of its cells and from its apparent slow growth. In tumors of this group, proliferation takes place by amitotic cell division and, as Bailey and Cushing have suggested, the tumors may be heterotropias.

Group 5.—This group is composed of the rather rare tumors of the pineal body which have been described by Horrax and Bailey [26] and the literature on which has been reviewed by Haldeman.[27] In Bailey and Cushing's scheme, they have been included under the terms of pineoblastoma and pineoloma, depending on the resemblance to the embryonic or to the adult pineal parenchyma.

COMMENT

In a general consideration of intracranial tumors, the author previously divided the gliomas into two large groups: the embryonic cell and the adult all types,[28] which embraces the foregoing classification in a condensed form. The conception, somewhat differently applied, was suggested by Carmichael,[29] whose line of division was not clearly drawn either from the standpoint of histogenesis or from that of gross morphology of the tumor. In general, tumors of the adult cell group have a good prognosis if they admit of surgical removal. Tumors of the embryonic cell group offer an increasingly good prognosis with their tendency to differentiate into adult elements.

The classification described in this study undoubtedly has its imperfections, but it seems more satisfactory than one in which the effort is

25. Bailey, P., and Bucy, P.: Oligodendrogliomas of the Brain, J. Path. & Bact. **32**:735, 1929.

26. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, Arch. Neurol. & Psychiat. **13**:423, 1925.

27. Haldeman, K. O.: Tumors of the Pineal Gland, Arch. Neurol. & Psychiat. **18**:724, 1927.

28. Courville, C. B.: Intracranial Tumors: Their Pathology, Symptomatology, Diagnosis and Prognosis, to be published.

29. Carmichael, E. A.: Cerebral Gliomata, J. Path. & Bact. **31**:493, 1928.

made to place each type under a single stage in the histogenic process. This cannot be done either from the standpoint of the most primitive or from that of the most advanced type of cell, for in either case overlapping must occur. In the groups that I have been able to study, the classification fits with a reasonable degree of accuracy the tumors that have a similar tissue architecture. This must be the ultimate criterion in any classification, for to be useful any nomenclature must suit the needs of the general pathologist, who cannot concern himself with the minutiae of all portions of the field of tumor pathology.[30]

The consideration of atypical or transitional forms, as has been suggested by Bailey,[18] does not militate against the scheme; in fact, the scheme has helped in the more accurate placing of certain individual gliomas that I have encountered. Furthermore, the predominance of a certain type of cell, either of glioblastic or neuroblastic type, should not be a cause for confusion, for such variations are the rule in neoplastic proliferations elsewhere in the body. Bailey and Cushing found a variation in the proportion between the glioblasts and neuroblasts in the medulloblastomas, showing that they do not follow any prescribed course in their formation. This is undoubtedly true of other tumors, and in the end the few cases in which the observations do not coincide with the usual ones must be judged on their tendencies and resemblances as a whole.

A possible objection to this scheme of classification which must be considered is that illustrated by cases not infrequently described in which there is an apparent transformation of a benign glioma into a more malignant one. The modus operandi of this change is difficult to conceive until it is decided whether gliomas have their origin in embryonic cells, according to the theory of Cohnheim, or whether they result from the assumption of embryonal characteristics by adult cells, as suggested by Ribbert. It is difficult to interpret the presence of neuroblasts in a glioma by Ribbert's hypothesis, for it seems most unlikely that cells as highly differentiated and specialized as the nerve cells can form apolar, unipolar or bipolar neuroblasts. As far as the gliomas are concerned, the weight of evidence seems to be in favor of their origin from embryonal cell "rests." If this is true, the malignant transformation from benign gliomas may be due to activity of undifferentiated portions of the tumor or the arousal of adjacent latent undifferentiated cells. This is in accord with the frequent observation of areas of embryonal type in benign forms and vice versa. It is evident that present knowledge does not permit the drawing of positive conclusions, and the ultimate solution of the problem must await further observations

30. Courville, C. B., and Adelstein, L. J.: Histologic Diagnosis of Tumors of the Glioma Group, California & West. Med., to be published.

and experimentation. There is little at hand to be used as argument against the classification proposed. The conception presents a slightly different aspect of the problem and may lead to the development of further important details of the histogenesis of this group of neoplasms.

SUMMARY

Based on the study of the cell types in a series of fifty gliomas, a classification of tumors of the group is suggested, which is based on the course of development of the constituent cells. In the embryonal gliomas, the differentiation of the various elements is compared to stages in normal neurohistogenesis as it is now understood. The histologic aspects of the tumor are dependent on the stage reached in the histogenesis of the fundamental cell and the location of the hypothetical "mother cell" when it assumed neoplastic activity. Regressive changes may also alter the primary appearance of the tumor.

The embryonal gliomas seem to be composed of undifferentiated cells that are bipotential, being capable of forming either glioblasts or neuroblasts in the course of their development. Such cells pass through various stages suggestive of normal neurohistogenesis.

THE EFFECT OF INJURY ON CELLULAR PERMEABILITY TO WATER*

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Permeability to water is a property of cells in general. It may be defined as the amount of water that enters or leaves the cell per unit of time, per unit of cell surface and per unit of osmotic driving force. In previous communications, it has been shown that permeability of the living cell to water is affected by a number of factors, such as temperature and chemical composition of the medium.[1] In this paper, we shall present evidence that injury to the cell is yet another factor causing alteration of its permeability to water.

For a study of the relation of injury to permeability, it is obviously necessary to select a cell permitting both recognition of injury by decisive criteria and precise measurement of permeability. The spherical unfertilized egg of the sea urchin, *Arbacia punctulata,* is admirably suitable. Injury is readily recognized on the addition of sperm after the cells have been returned to their natural medium, sea water, at the conclusion of an experiment; normal cells shortly undergo cleavage, while injured cells divide atypically or not at all.

METHOD OF MEASURING PERMEABILITY OF CELL TO WATER

Permeability of the cell to water is determined by the following method:[2] Cells from a single specimen of *Arbacia* are placed in sea water of the desired osmotic pressure,[3] at constant temperature. In hypotonic solution, water enters under the driving force of osmotic pressure, and the cell swells; conversely, the

* Submitted for publication, June 6, 1930.

* From the Laboratory of Pathology, School of Medicine, University of Pennsylvania, Philadelphia, and the Marine Biological Laboratory, Wood's Hole, Mass.

1. McCutcheon, M., and Lucké, B.: The Kinetics of Osmosis in Living Cells, J. Gen. Physiol. **9**:697, 1925-1926; The Effect of Certain Electrolytes and Non-Electrolytes on Permeability of Living Cells to Water, ibid. **12**:129, 1928. Lucké, B., and McCutcheon, M.: The Effect of Valence of Ions on Cellular Permeability to Water, ibid. **12**:571, 1929.

2. For details of method see: McCutcheon and Lucké (footnote 1, first reference) and Lucké and McCutcheon (footnote 6).

3. In this paper, the concentration of the sea water is expressed in per cent of isotonic (100 per cent) sea water. Thus 60 per cent sea water means a solution consisting of 60 parts of sea water and 40 parts of distilled water.

cell shrinks when placed in a solution hypertonic with respect to the cell's interior. The changes of volume proceed relatively slowly and permit accurate measurement of the diameter at intervals of a minute with a filar micrometer. Since the cells are spherical, diameters are easily converted to surface area and volume. The course of change in the volume is satisfactorily described by certain equations by which permeability may be computed.[4] For this purpose, the mean volume of several cells (generally six) is plotted against time, and a smooth curve drawn through the points (chart 1). The rate of passage of water is given by the rate of change in volume, and is obtained from the slope of the curve at a given time (by drawing a tangent to the smooth curve). This value is divided by cell surface and the difference in pressure between the interior of the cell and the medium. The resulting numeric quantity is termed the permeability of the cell to water, at a given time; the units here used are cubic microns of water per minute, per square micron of cell surface, per atmosphere of pressure.[5]

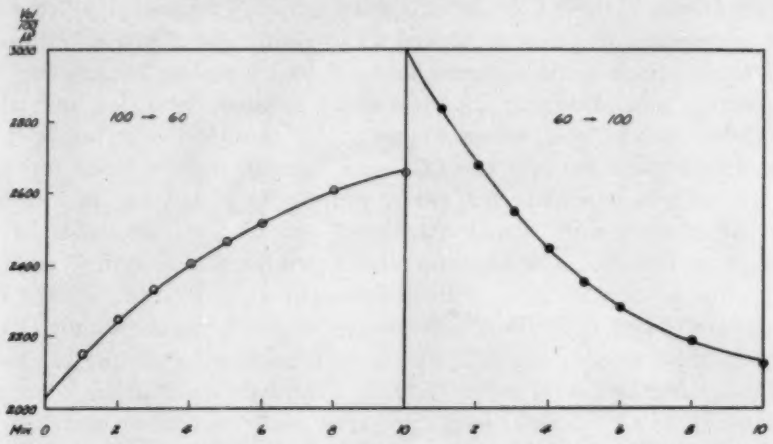

Chart 1.—Graphs illustrating the course of swelling and of shrinking of living uninjured cells in anisotonic solutions at constant temperature (18 C.). The mean volume of six cells is plotted against time. The left graph shows the course of swelling (endosmosis of water); cells removed from their natural medium (100 per cent sea water) were placed in 60 per cent sea water, and measured at intervals of one minute. In the right graph, shrinking (exosmosis of water) is illustrated. Cells were first allowed to swell in 60 per cent sea water for forty-five minutes; the swollen cells were then transferred to 100 per cent sea water, and measured at intervals of one minute.

4. McCutcheon and Lucké (footnote 1, second and third references).

5. Mathematically expressed,

$$\text{Permeability} = \frac{\frac{dV}{dt}}{S \cdot (P - P_{ex})}$$

where $\frac{dV}{dt}$ is the rate of passage of water into or out of the cell (and hence the rate of change of volume), S is the area of the cell surface, P the osmotic pressure of the interior of the cell, P_{ex} the osmotic pressure of the external medium and $(P - P_{ex})$ the difference in osmotic pressure between the interior of the cell at time *t*, and the medium. S is computed directly from the volume (V) read from the curve at time *t*. P is calculated from the equation $P_o \cdot V_o = P \cdot V$,

By the method described, we have studied the permeability to water of cells injured by exposure to heat and by exposure to anisotonic solutions.

THE EFFECT OF INJURY BY HEAT ON PERMEABILITY TO WATER

Cells were placed in sea water of different temperatures (constant to ± 1 C.) for a given number of minutes. After being cooled in sea water at room temperature, they were transferred to a hypotonic solution and measured at intervals of one minute. In a previous study, we had found that exposure to temperatures of 52 and 60 C. causes irreversible gelation of protoplasm and increase of volume in isotonic solution.[6] In the range of temperature employed in the present experiments (from 30 to 45 C.), the cells were definitely injured or killed, but the protoplasm was not so altered as to lead to swelling in ordinary sea water. Such cells, however, retained their property of swelling in hypotonic, and shrinking in hypertonic, solution, provided that the exposure to heat was not prolonged. For example, cells heated for less than sixteen minutes at 44 C. were injured, but remained capable of swelling in hypotonic sea water, while cells heated for as long as sixteen minutes were firmly coagulated and rendered incapable of a change in volume. The behavior of these injured cells differs greatly from that of normal cells. This is shown in chart 2. Cells injured by heat were placed in different hypotonic solutions; it may be seen in chart 2 that they swelled rapidly for several minutes, after which they shrank. Normal cells under similar conditions swell until constant volume (i. e., equilibrium) is attained after many minutes or even hours, or until they burst, having reached their elastic limit.

From experiments of this kind it is apparent that injured cells do not lose their semipermeability at once or completely. In injured as in normal cells, the degree of the change in volume varies inversely with the osmotic pressure of the medium, being greatest in the most dilute solution. But while in normal cells the amount of dissolved substances that can enter or leave the cell is inappreciable under the conditions of the experiments, in injured cells escape of contents takes place and the cell may shrink, though in a hypotonic medium.

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where P_o is the osmotic pressure of ordinary sea water (taken as 22 atmospheres), V_o the volume of the cell in its natural medium, V the volume at a given time, and P the osmotic pressure inside the cell at a given time. (For further details see McCutcheon and Lucké [footnote 1, second and third reference].) This differential equation is used in its integrated form in "Further Studies on the Kinetics of Osmosis in Living Cells," to be published. In this paper, a theoretical treatment of osmosis is given.

6. Lucké, B., and McCutcheon, M.: Reversible and Irreversible Swelling of Living and of Dead Cells, Arch. Path. **2**:846, 1926.

Experiments were now planned to determine whether quantitative differences exist between injured and normal cells in regard to permeability to water.

In the first group, we varied the length of time during which cells were exposed to heat. The results of a typical experiment are shown in table 1. Here cells exposed to a temperature of 39 C. for different periods were caused to swell in a hypotonic solution. The table shows

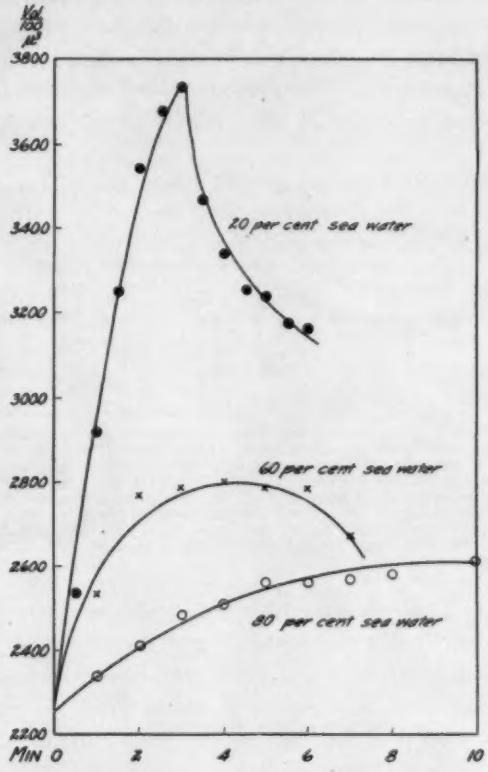

Chart 2.—The effect of injury by heat on permeability to water. Cells placed for four minutes in ordinary sea water heated to 44 C. were transferred to several hypotonic solutions (20, 60 and 80 per cent sea water) and measured at intervals of one minute. The mean volumes of three cells are plotted against time. It is seen that the injured (or dead) cells swell rapidly in 20 and 60 per cent sea water and then shrink, though in a hypotonic medium.

that permeability to water varies directly with the length of exposure to injury. This relation is most clearly brought out in the initial measurements, before further changes occurred in the cell membrane. Thus the values of permeability determined at the first minute of the swelling process form a regular series, cells heated for two minutes

having the lowest permeability (0.076), while those heated for sixteen minutes showed an increase in permeability of almost 300 per cent over the unheated controls. The initial increase in permeability may be followed by a further increase, or the gradual escape of dissolved substances from the injured cells may lead to an apparent decrease.

In the next group, the temperature was varied and the time of exposure held constant. It was again found that permeability to water varied with the intensity of the injurious factor. A typical experiment is represented in table 2. Here cells were exposed for four minutes to different temperatures, and then caused to swell in a hypotonic solution. It may be seen that exposure to 39 C. causes an increase in permeability,

TABLE 1.—*The Effect of Exposure to 39 C. for Varying Lengths of Time on Permeability to Water* *

Intervals at which Permeability was Calculated	Permeability Following Increasing Periods of Exposure					
	0	2 Min.	4 Min.	8 Min.	12 Min.	16 Min.
1.....	0.069	0.076	0.081	0.084	0.119	0.172
2.....	0.072	0.080	0.080	0.090	0.119	0.093
3.....	0.074	0.078	0.079	0.099	0.104	0.058
4.....	0.070	0.070	0.079	0.108	0.083	.....
5.....	0.068	0.066	0.075	0.119	.....	.....

* Time of exposure is given in the top line; 0 exposure is the control experiment. The solution in which the cells were caused to swell after exposure was 40 per cent sea water at 20 C. The values of permeability were determined for successive minutes, and represent the number of cubic microns of water entering the cell per minute per square micron of cell surface, per atmosphere of pressure. It is seen that at the first minute (before further changes had occurred in the cell membrane) the values for permeability form a regular series and vary directly with the length of exposure to the injurious agent; at later minutes irregularities in values develop. Fertilization tests showed atypical division after two minutes' exposure, and no cleavage after longer exposure.

exposure to 41 C. a still greater increase, while exposure to 45 C. brings about coagulation, so that permeability can no longer be measured.

From these and similar experiments the conclusion may be drawn that injury of cells by heat manifests itself by an increase in permeability to water, and that this increase is proportional to the degree of injury.

INJURY BROUGHT ABOUT BY EXPOSURE TO ANISOTONIC SOLUTIONS

When cells are placed in hypotonic solutions of different osmotic pressures, the rate of increase in volume is of course very different, being most rapid in the most dilute solution and slowest in the least dilute. But when the rates for entrance of water are divided by osmotic driving force and cell area, these differences disappear; permeability to water, at least for the first several minutes is independent of the osmotic pressure of the medium. At later minutes, however, differences in permeability may appear in the sense that while there is a slight decrease

in permeability in higher concentrations,[7] there is a marked increase in lower concentrations. When the cells are returned to ordinary sea water and inseminated, it is found as a rule that in cases in which permeability has increased, cleavage fails or is atypical, whereas in cases in which permeability has not increased, there is no prevention of subsequent normal cleavage. It is believed that increased permeability in such experiments is an expression of injury due to too rapid entrance of water. An experiment illustrating this case is recorded in table 3. In this experiment, permeability was calculated at successive minutes for

TABLE 2.—*The Effect of Four Minute Exposures to Varying Temperatures on Permeability to Water*

Degrees of Temperature, C....	20	31	36.5	39	41	45
Permeability.....	0.089	0.091	0.083	0.117	0.137	Coagulated

The concentration of sea water employed for swelling was 50 per cent at 20 C. The values of permeability were calculated for each series at the third minute. It is seen that exposure to 39 and 41 C. causes an increase in permeability.

TABLE 3.—*Permeability to Water Calculated at Successive Minutes for Cells in 30, 40 and 50 Per Cent Sea Water*

Intervals at which Permeability was Calculated, Min.	Permeability in Various Concentrations of Sea Water		
	30%	40%	50%
2.....	0.086	0.069	0.069
3.....	0.089	0.068	0.069
4.....	0.092	0.064	0.062
5.....	0.098	0.063	0.064
6.....	0.103	0.063	0.060
8.....	0.117	0.076	0.058
10.....	.....	0.097	0.056
Cleavage.....	All cytolyzed	50% divided; of these one-half atypical	All divided; 90% typical

The values give the number of cubic microns of water entering the cell, per square micron of surface, per atmosphere of pressure. The cells in 30 per cent sea water are injured from the beginning and give high values of permeability, which increases from minute to minute; in 40 per cent sea water, permeability increases after the sixth minute, owing to injury; the values for permeability of cells in 50 per cent sea water are normal.

cells in three different hypotonic solutions. In 50 per cent sea water, permeability was normal, i. e., it declined slightly; subsequently, all cells underwent cleavage, which was normal in nine-tenths of the cells. In 40 per cent sea water, permeability was the same as in the preceding dilution for six minutes; then it rapidly increased. Subsequently, only one half of the cells divided and one half of these were atypical. In 30 per cent sea water, permeability was high from the start (this is unusual) and increased continually; no cells remained capable of cleavage, all eventually undergoing cytolysis.

7. This decrease is due, at least in part, to the fact that osmotically inactive substances within the cell are neglected in the present method of calculation.

We now come to a much more favorable type of experiment for demonstrating the relation of permeability to injury by hypotonic solutions. Under the conditions just described, injury occurs only after several minutes and therefore does not affect the initial permeability of the cell. We shall now describe experiments in which unheated cells previously swollen in various hypotonic solutions are returned to ordinary sea water and allowed to shrink. In such cases, the injury has been inflicted, if at all, during the swelling process, and therefore might be expected to affect the rate of shrinking from the first instant.

TABLE 4.—*The Effect of Exposure to Hypotonic Solutions of Varying Degree on Permeability of Normal Cells*

Concentration of Sea Water, %	Permeability	Per Cent Typically Divided
30	0.123	95
35	0.136	95
40	0.135	95
45	0.139	95
55	0.113	95
60	0.139	95

Cells were swollen for seven minutes in 30, 35, 40, 45, 55 and 60 per cent sea water, and then returned to isotonic sea water. The course of exosmosis of water was studied at 14 C. Permeability was calculated at the third minute. The values of permeability show no drift. On subsequent fertilization, 95 of 100 cells divided normally in all cases.

TABLE 5.—*The Effect of Exposure to Hypotonic Solutions of Varying Degree on Permeability of Injured Cells*

Concentration of Sea Water, %	Permeability	Cleavage
35	0.330	Mostly cytolyzed; 10 per cent atypically divided
40	0.227	Many cytolyzed; 25 per cent atypically divided; 25 per cent typically divided
50	0.183	70 per cent typically divided; rest not divided
55	0.216	80 per cent divided of which one-fourth are atypical
60	0.107	80 per cent divided, all typical

Cells swollen for seven minutes in the various hypotonic solutions were returned to isotonic sea water and exosmosis of water studied at 18 C. Permeability was calculated at the third minute. The values of permeability are high (except in 60 per cent of sea water), and vary with the degree of injury as shown by the fertilization tests.

Before citing an example of this type of injury, it should be pointed out that such injury may often be avoided, even in very dilute solutions, provided that the solution is at low temperature (from 10 to 15 C.), exposure is not too prolonged, and the cells are in good condition to start with. Under these conditions when cells previously swollen in various hypotonic solutions are returned to ordinary sea water and allowed to shrink, the permeability in shrinking is found to be independent of the osmotic pressure of the solution used to induce swelling. Corresponding fertilization tests are normal. The data on an experiment illustrating this are given in table 4. Cells previously swollen for seven minutes in six different hypotonic solutions were caused to shrink in ordinary sea water. The values of the perme-

ability of cells from the several different solutions show no drift, and in all cases 95 of 100 cells subsequently divided normally.

A strikingly different result was obtained if injury occurred during the swelling process. In table 5 is recorded an experiment in which cells were allowed to swell for seven minutes in five different hypotonic solutions. When the cells were returned to isotonic solution, permeability [8] was found to vary from 0.107 in cells caused to shrink from 60 per cent sea water, to 0.330 in cells caused to shrink from 30 per cent sea water, a difference of threefold. A corresponding difference was observed in the results of insemination, though there was evidence of slight injury even in the 60 per cent cells.

A final typical experiment is recorded in table 6. Here cells were kept for four and a half hours in several hypotonic solutions, and then caused to shrink in isotonic sea water. In four of the dilutions, perme-

TABLE 6.—*The Effect of Exposure to Various Hypotonic Solutions for Four and Five-Tenths Hours on Permeability*

Concentration of Sea Water, %	Permeability	Cleavage
50	0.150	30 per cent divided; rest cytolyzed
55	0.083	90 per cent typically divided
60	0.089	95 per cent typically divided
65	0.093	95 per cent typically divided
70	0.094	95 per cent typically divided

Cells swollen for four and one-half hours in various hypotonic solutions were then returned to isotonic sea water, and exosmosis of water studied at 18 C. Permeability was calculated at the third minute. It is seen that the long exposure did not cause injury, except in the 50 per cent dilution. The values of permeability are normal, except those for the injured cells, which are high.

ability was normal, and fertilization tests showed no injury. In the most dilute solution, the cells were injured and had high permeability.

From these and similar experiments it is apparent that injury of cells by hypotonicity of the medium manifests itself by increased permeability to water, and that this increase varies directly with the degree of injury as shown by fertilization tests.

COMMENT

Many investigators have studied the morphologic alterations of cells injured by a variety of agents. The functional properties of injured cells have received much less attention. Of these, the one most intensively studied in relation to injury is permeability of the cell to dissolved substances. With a variety of material and by several different methods, the conclusion has been reached that injury renders

8. As has been stated, permeability varies but little during the first several minutes of an experiment; as a matter of convenience, permeability was calculated at the third minute. The values thus obtained agree closely with the values obtained by the integrated equation (see footnote 5).

cells more permeable to different substances that normally are prevented from entering or leaving the cell.[9] However, little precise information is available on abnormal permeability to water. One such investigation is that of Landis, who found that injury to capillaries markedly increased their permeability to water.[10] Landis here dealt with the transport of water across the capillary wall; in the present experiments, we are concerned with the permeability of cells themselves.

It is a well known fact that while cells are normally permeable to water, the degree of permeability is a somewhat restricted one, so that water enters or leaves the cells relatively slowly.[11] In the present experiments, it has been shown that injury to the cell increases its permeability to water. The results of our experiments are in harmony with studies of other investigators on permeability to dissolved substances.

SUMMARY

The unfertilized egg of the sea urchin, *Arbacia punctulata,* was used as a cell in which injury can readily be recognized and permeability to water accurately measured.

It was found that injury (induced by high temperature and by anisotonic solutions) causes a marked increase in cellular permeability to water, and that this increase in permeablity can be correlated with the degree of injury.

The method described affords a convenient measure of injury.

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9. Osterhout, W. J. V.: Injury, Recovery, and Death, in Relation to Conductivity and Permeability, Philadelphia, J. B. Lippincott Company, 1922; Exosmosis in Relation to Injury and Permeability, J. Gen. Physiol. **5**:709, 1923. Brooks, S. C.: Conductivity as a Measure of Vitality and Death, ibid. **5**:368, 1923.

10. Landis, E. M.: Micro-Injection Studies of Capillary Permeability: I. Factors in the Production of Capillary Stasis, Am. J. Physiol. **81**:124, 1927; II. The Relation Between Capillary Pressure and the Rate at which Fluid Passes Through the Walls of Single Capillaries, ibid. **82**:217, 1927.

11. Northrop, J. H.: Kinetics of the Swelling of Cells and Tissues, J. Gen. Physiol. **11**:43, 1927.

TRUNCUS SOLITARIUS PULMONALIS

A RARE TYPE OF CONGENITAL CARDIAC ANOMALY *

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From time to time, a congenitally anomalous heart is found that possesses only a single arterial trunk. Abbott [1] collected twenty-three such cases. It is usually a heart that is severely deformed, biloculate or triloculate, with many other defects associated with the arterial one.

At first glance, the single arterial trunk would be considered as a persistent truncus communis, in which the original common arterial trunk issuing from the bulboventricular loop had failed to divide into its appointed aortic and pulmonic parts. But cases of the latter are, indeed, rare. I have been able to find only two that may be accepted, one reported by Preisz [2] in 1890, and the other more recently by Santa Cruz.[3] Incomplete division of the common trunk is seen much more frequently than this total failure to divide.

In most of the cases of single arterial trunk that are regarded as cases of truncus communis, complete division has occurred. But subsequently one side involutes, leaving the other to carry the load of both. The single vessel remaining is therefore not a truncus communis, but a truncus solitarius which has lost its partner. Such mishaps can readily occur. When, as in the case to be described, there is a large defect in the ventricular septum, flow relationships are so disturbed that the aorto-pulmonary septum develops irregularly. The passage of the bulk of the the circulation through one trunk still further reduces the other until the latter may be completely, or almost completely, obliterated. Then only a small vestige of the second vessel or no trace of it may be found.

Usually, the pulmonic side is obliterated, and the single vessel left behind is a truncus solitarius aorticus. Several such cases have been reported.[4] The solitary trunk is identified as the aorta by the origin of

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* From the Department of Pathology of the Cook County Hospital.

1. Abbott, M., in Osler, W.: Modern Medicine, Philadelphia, Lea & Febiger, 1925.

2. Preisz, H.: Beiträge zur Lehre von den angeborenen Herzanomalien, Beitr. z. path. Anat. u. z. allg. Path. **7**:247, 1890.

3. Santa Cruz, J. Z.: Common Ventricular Opening for Aorta and Pulmonary Artery, J. Philippine Islands M. A. **5**:295, 1925.

4. Moenckeberg, J. G.: Die Missbildungen des Herzens, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2. Dickson, W. E.: A Congenital Abnormality of the Heart and Blood Vessels, J. Anat. & Physiol. **48**:210, 1910.

the coronary arteries from behind the semilunar cusps. The lungs are then supplied by branches arising directly from the aortic trunk or by the ductus botalli or by the bronchial arteries or by anomalous branches from the great vessels of the neck.

Much more rarely does the aortic side involute and leave a truncus solitarius pulmonalis. In this case, the sinuses of Valsalva are free from coronary openings. Abbott [1] referred to such a case described by Farre and to another by Forster. In each a single, large vessel, the pulmonic trunk, arose from the ventricle and was connected to the transverse aorta by a widely patent ductus arteriosus. This trunk gave off the pulmonary arteries, while the great vessels of the neck and arms arose from the beginning of the transverse aorta. They then described "a single vessel arising from the concavity of the aortic arch, and running down alongside the pulmonic trunk to the base of the heart, where it divided into two coronary vessels." This was evidently the vestige of the ascending aorta.

Recently, I studied a case of truncus solitarius aorticus,[5] with particular reference to Spitzer's theory of detorsion defect.[6] For comparison, and also because of its greater rarity, I report the following case of truncus solitarius pulmonalis.

A colored boy, R. H., was born in a spontaneous, normal delivery at full term. The mother was a healthy, young primipara, 18 years of age. Her Wassermann reaction was negative. The child lived for only four days, and died with the clinical diagnosis of bilateral bronchopneumonia.

The heart weighed 30 Gm., as compared with the normal weight at birth of 24 Gm. It lay in normal position, but was made up almost entirely of the large right ventricle and the large right auricle. There was an intervening, well developed tricuspid valve with its three groups of chordae tendineae. The chambers on the left side of the heart were insignificantly small and only a single, large arterial trunk, 27 mm. in diameter, issued from the base of the heart

No coronary artery sprang from it. The orifice of the trunk was guarded by three semilunar cusps that, according to their position, could be termed as left, anteroright and posteroright. As the single trunk ascended it gave off the two pulmonary arteries from its anteroleft aspect. It then continued in a widely open, funnel-shaped communication with the transverse aorta. At its insertion was a stump of isthmus aortae from which, crowded together, arose the innominate, the left common carotid and the left subclavian arteries.

Just distal to its insertion, a single, small artery, 1 mm. in diameter, took origin from the aortic arch. It ran down the posteroleft aspect of the large arterial trunk and behind the origin of the pulmonary arteries, to divide at the base of the heart into an anterior descending and a left circumflex coronary branch. No trace of the ascending aorta could be found other than this vessel which gave off distally

5. Shapiro, P.: Detorsion Defects in Congenital Cardiac Anomalies, Arch. Path. **9**:54, 1930.

6. Spitzer, A.: Ueber den Bauplan des normalen und missbildeten Herzens, Virchows Arch. f. path. Anat. **243**:83, 1923.

the branches of the left coronary artery and which was entirely independent of the large arterial trunk beside it. There was no right coronary artery. The left supplied the whole heart.

The wall of the large right ventricle was 5 mm. thick. From the left aspect of the large arterial trunk, there projected into the anterior upper corner of the

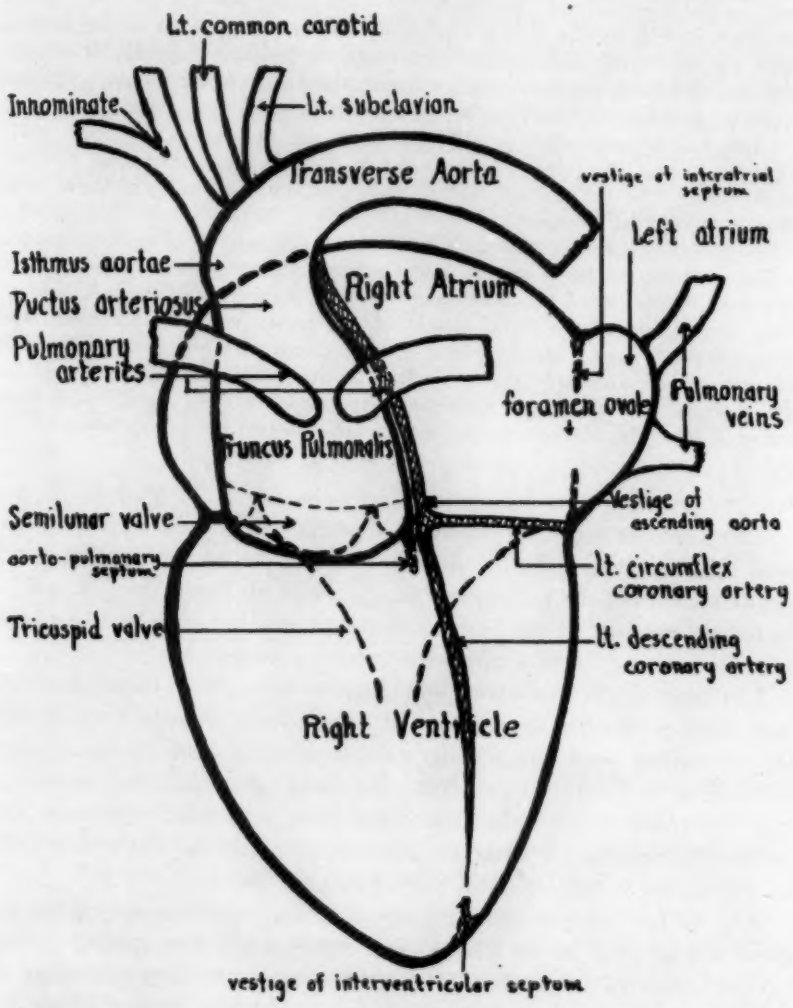

Fig. 1.—Diagram of heart showing truncus solitarius pulmonalis and other anomalies.

ventricular chamber a small ridge of the aortopulmonary septum. A small ridge also of interventricular septum was barely discernible at the apex of the large ventricular cavity. The rest of the interventricular septum was absent. A widely open septal defect led from the huge right ventricle into the insignificant left one.

The cavity of the large right auricle was 22 mm. in diameter. The inferior and superior venae cavae and the coronary sinus opened into it normally. It had a well developed auricular appendage. The pulmonic veins emptied by two trunks, instead of the usual four, into the left auricle. The small left auricle was an antechamber to the large right one. It was only 3 mm. deep, but carried also a small auricular appendage. Inferiorly, its walls fused into the left wall of the common ventricle, so that it was completely cut off below from communication. There was no mitral orifice. The mitral leaflets, their three groups of chordae tendineae, and their papillary muscles had all been lost in the fusion. The left auricle emptied into the right auricle only by an open foramen ovale 7 mm. wide.

There was no crepitation in the right upper and in most of the right middle and lower lobes. The left lower and most of the left upper lobes were similarly noncrepitant. The cut surface showed numerous confluent granular areas from which pus could be expressed.

The other organs showed nothing unusual.

The anatomic diagnosis was: Truncus solitarius pulmonalis; persistent ductus arteriosus; hypoplasia of the ascending aorta, with persistence of the left coronary artery and atresia of the right; origin of the great vessels of the neck from isthmus aortae; atresia of the mitral orifice; patent foramen ovale; incomplete inclusion of the pulmonary vein in the wall of the left auricle; hypoplasia of the left uricle and vestigial left ventricle; hypertrophied right auricle and right ventricle; defective interventricular septum, and bilateral bronchopneumonia.

COMMENT

This case corresponds closely to those of Farre and Forster. The small vessel running from the aortic arch down the left side of the ductus arteriosus, behind the pulmonary arteries, and on down the left side of the pulmonic trunk to the base of the heart was the only vestige of the ascending aorta. From it arose the coronary artery.

The large single trunk was pulmonic, for it had no coronary arteries. Cases are described in which, because of abnormal aortopulmonary division, the coronary arteries arise by a common trunk from the aorta. One coronary artery may spring from the aorta and the other from the pulmonic trunk. But never has there been reported a shift of both coronaries from the aortic to the pulmonic side. An arterial trunk without coronaries is not an aorta, but a pulmonic trunk.

Except for the coronary supply that was still maintained by the aortic vestige, the blood flow to the entire body was carried by the truncus solitarius pulmonalis. It filled the lesser circulation through its pulmonary arteries, and then carried the systemic flow through the ductus botalli to the transverse aorta and its branches. It was therefore rather large. But it was truncus solitarius and not a truncus communis, for it was guarded by three semilunar cusps and not by four. The aortopulmonary division had already taken place.

In the original truncus communis, four proximal endocardial buds develop at the common arterial orifice. There are a large pair and a small pair. If development stops at this early stage, if the truncus

communis persists, the single arterial trunk arising from the heart is left with its four endocardial swellings to form four semilunar cusps. Thus von Huelse,[4] Gierke and Abbott have emphasized that a single arterial trunk may be considered a true truncus communis only if it has four semilunar cusps (fig. 2*a*).

If development goes on, fusion of the apposing larger pair of buds forms the aortopulmonary septum (Tandler[7]). But in forming this septum, the pair of large buds is divided into four. These, with the undivided pair of small buds, make a total of six, from which six semilunar cusps are hollowed out, three for the aorta and three for the pulmonic trunk (fig. 2*b*). This is the normal definite state. If one side then subsequently involutes, it carries away with it three of the cusps. The solitary trunk remaining is left with only its own three cusps (fig. 2*c*).

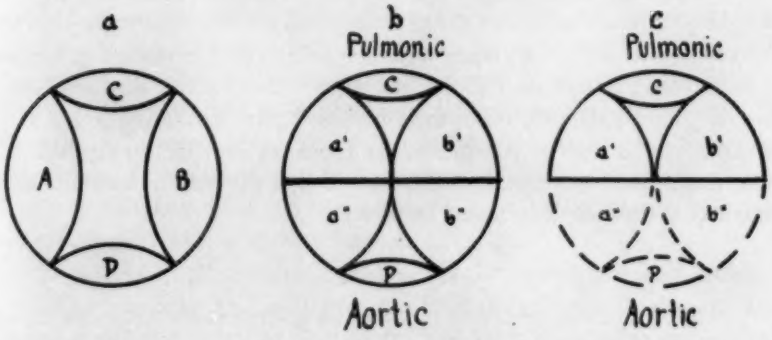

Fig. 2.—Diagram of orifices of truncus communis (*a*), normal aorta and pulmonary artery (*b*) and truncus solitarius (*c*).

Evidence that division had taken place in the case described was the vestige of aortopulmonary septum that projected from the left wall of the pulmonic trunk into the anterocranial corner of the large ventricular chamber. The common trunk had divided. But the aortic side had then almost completely involuted and was retained only as a small vessel for the coronary supply. The remaining pulmonic trunk with its allotted three semilunar cusps was left as a truncus solitarius to supply the whole body.

This defect was accompanied by so many other severe cardiac abnormalities as to indicate a grave deficiency in cardiac growth vitality. It is Spitzer's theory that the landmark and primary mechanism of such deficiency is a defect in the normal clockwise torsion of the pulmonic

7. Keibel, F., and Mall, F.: Human Embryology, Philadelphia, J. B. Lippincott Company, 1912.

trunk about the aortic. In the formation of the definitive mammalian heart, the pulmonic trunk swings from above posterior to the aorta, down to the left and anteriorly to take its position in front of the aorta as they issue from the heart. When the vis á tergo of cardiac growth is reduced, this torsion partly or completely fails. The greater the defect in torsion, the more severely anomalous is the heart.

It was difficult to estimate detorsion in this case, but there were three signs of it to suggest a basis for the numerous anomalies encountered. The semilunar cusps of the pulmonic trunk were abnormally placed. There was a left, an anteroright and a posteroright, instead of the normal right, left and anterior. But which cusp correspond to which cannot be stated with certainty. If it had been the aorta, the noncoronary cusp would have served as a guide. Here, however, all the cusps were noncoronary.

A second sign of detorsion was the origin of the pulmonary arteries from the anteroleft aspect of the pulmonic trunk. Normally, they should come off posteriorly. The third was the position of the vestige of ascending aorta on the left of the ductus botalli and behind the pulmonary arteries. Normally this relation is reversed; the ascending aorta is on the right of the ductus botalli and in front of the pulmonary arteries. These three facts indicate, at least, that in this severely anomalous heart a marked detorsion defect had occurred.

SUMMARY

A case of truncus solitarius pulmonalis is described. The distinction from truncus communis and from truncus solitarius aorticus is emphasized. There were numerous associated cardiac abnormalities and evidence that these were based on a severe detorsion defect.

THE DISTRIBUTION OF LIPOID IN A CASE OF NIEMANN-PICK'S DISEASE ASSOCIATED WITH AMAUROTIC FAMILY IDIOCY *

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The peculiar perversion of lipoid metabolism in Niemann-Pick's disease has in recent years aroused considerable interest. The clinical and anatomic features of the disease have been amply elucidated and its differentiation from Gaucher's disease established. Whereas in Gaucher's disease kerasin has been identified as a lipoid specific for this condition, the scattered chemical analyses of spleens in Niemann-Pick's disease suggest merely a general increase of the normal lipoids, especially of phosphatids and cholesterol. The distribution of lipoid in the few livers analyzed has shown a similar tendency.

When a case of Niemann-Pick's disease associated with amaurotic family idiocy came to autopsy in this hospital, we undertook the study of the lipoid chemistry of the spleen and liver. We also included that of the brain because of the interest in the relationship of amaurotic family idiocy (Tay-Sachs) to morbus Niemann-Pick.

REPORT OF CASE

History.—A girl, 10 months of age, weighing 5,000 Gm., of Jewish parentage, was admitted to the service of Dr. Béla Schick on April 15, 1929, with a history of retarded development for three months, loss of weight and difficulty with feeding. The child was born of a first pregnancy, in a normal delivery, and was breast fed until she was 7 months of age. She had had chickenpox at 7 months; otherwise the past history was negative.

Physical Examination.—The patient showed enlargement of the spleen and the liver down to the umbilicus, peculiar red spots in the maculae of both eyes and brownish pigmentation of the skin. A tentative diagnosis of Niemann-Pick's disease was made. This diagnosis was confirmed by splenic puncture.

Laboratory Data.—The blood chemistry was: total fat 1,430 mg., cholesterol 290 mg., serum calcium 12.2 mg. and serum phosphorus 3 mg. per hundred cubic centimeters. The urine showed doubly refractive bodies. The blood showed mod-

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* From the Laboratories of Mount Sinai Hospital.

erate secondary anemia and mild polymorphonuclear leukocytosis. The most interesting cells in the blood smear were the lymphocytes, a large percentage of which contained vacuoles. The result of the Kahn test was negative.

Ophthalmologic and Psychiatric Examinations.—The ophthalmologist noted in the fundi a large oval grayish ring in the center of which was the bright red color of the macula, and diagnosed amaurotic family idiocy. The psychiatrist noted that the mentality of the child approached idiocy.

Course.—While the patient was in the hospital, a respiratory infection persisted, associated with bouts of fever and vomiting. After two months, the patient was

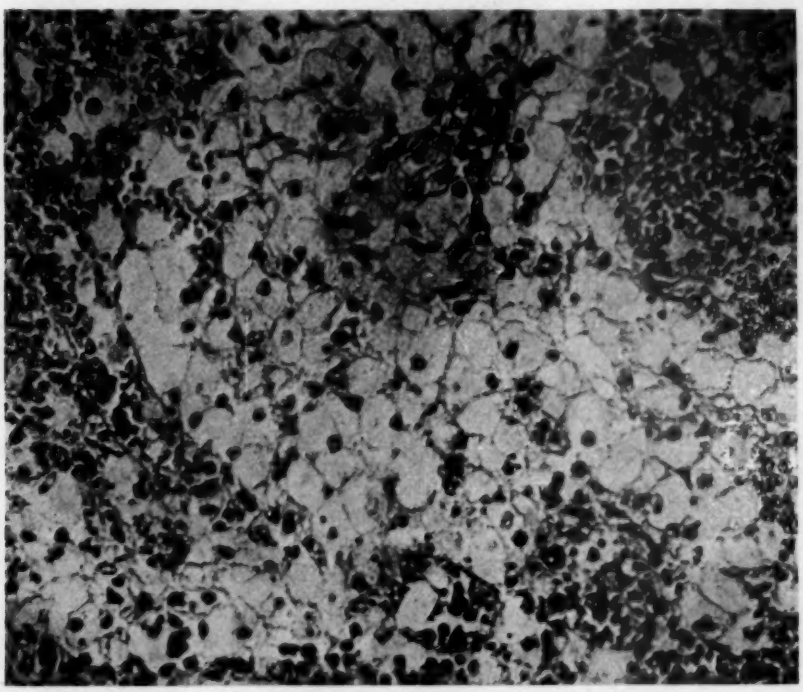


Fig. 1.—Section of spleen; hematoxylin-eosin stain.

taken home against advice, only to return on Sept. 5, 1929, with an exacerbation of symptoms and frank signs of pneumonia, culminating in coma and death. On the second admission, the child was markedly underdeveloped and malnourished. It presented a bronzed appearance, with extreme pallor and chronic emaciation. The anemia was more severe; the cherry red spots in the macula were again noted, as were the other signs typical of Niemann-Pick's disease observed during the previous admission to the hospital.

Pathologic Examination.—Dr. P. Klemperer supplied the following pathologic observations: The body was that of a poorly developed, emaciated, white female infant, measuring 68 cm. The spleen and liver were markedly enlarged, weighing 180 and 500 Gm., respectively. All the internal lymph nodes were enlarged and on section presented a distinct yellow color.

Microscopic examination of paraffin sections (figs. 1, 2 and 3) revealed the presence of large round or polygonal cells with diffuse vacuolization of the cytoplasm, throughout the spleen, between the liver cell cords, in the lymph nodes, within the alveoli of the lungs, as well as in the peribronchial and perivascular connective tissue, and, in smaller numbers, also in the alveolar septums. Not only the lymphadenoid tissue but also the stratum proprium of the mucosa of the intestines showed the presence of the same cells. The bone-marrow was diffusely infiltrated. The glomeruli of the kidneys contained the same cells. Sudan III did not stain the substance within the large cells, but sections stained according to the method of Lorrain-Smith-Dietrich revealed the presence of grayish-black stained

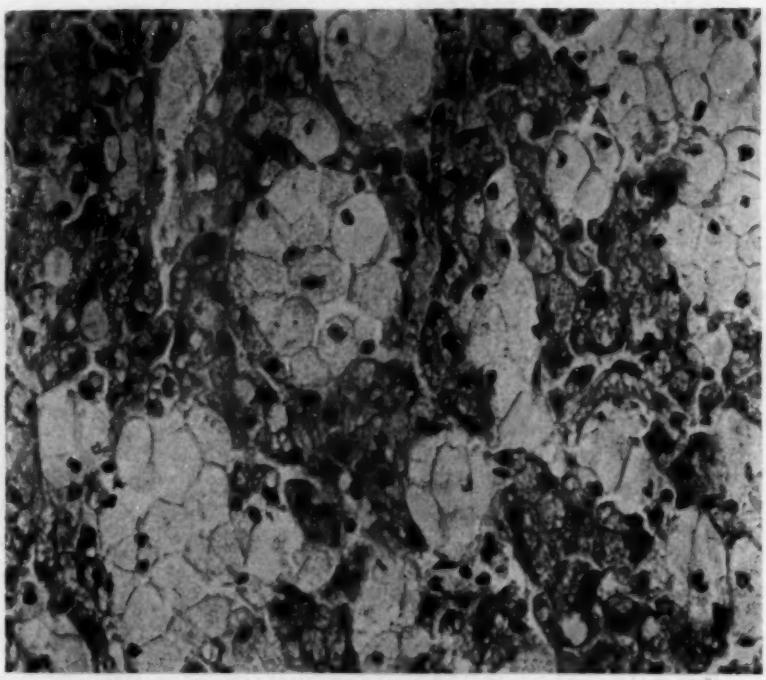


Fig. 2.—Section of liver; hematoxylin-eosin stain.

granules. Also sudan stain applied after fixation in potassium bichromate according to Ciaccio gave a positive result. Examination under polarized light showed the presence of small crystals, doubly refractive granules, so fine that the entire cell appeared as though filled with mist. The epithelium of the convoluted tubules of the kidney, however, contained, in addition to lipoid substances that stained only after the Smith-Dietrich method, small sudan stained droplets. From these microchemical staining reactions one can say that the large cells contained no neutral fat, but some doubly refractive lipoids, most probably cholesterol, and large amounts of lipoids that were neither neutral fats nor cholesterol.

The microscopic studies of brain and spinal cord by Dr. J. H. Globus [1] revealed alterations typical of amaurotic family idiocy. The monstrous and exceedingly

1. Globus, J. H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **85**:424, 1923.

large nerve cells, with swelling of the dendrites and loss of normal cytoplasmic structure (such as disappearance of fibrillae, accumulation of granules and displacement of nuclei) were uniformly found throughout all parts studied (fig. 4).

DISTRIBUTION OF LIPOID

The analysis of organs for lipoids can be carried out by a great variety of methods. Alkaline saponification of the material allows the most complete extraction of the derived lipoids as saturated and unsaturated fatty acids, cholesterol, etc., but such analysis does not allow any

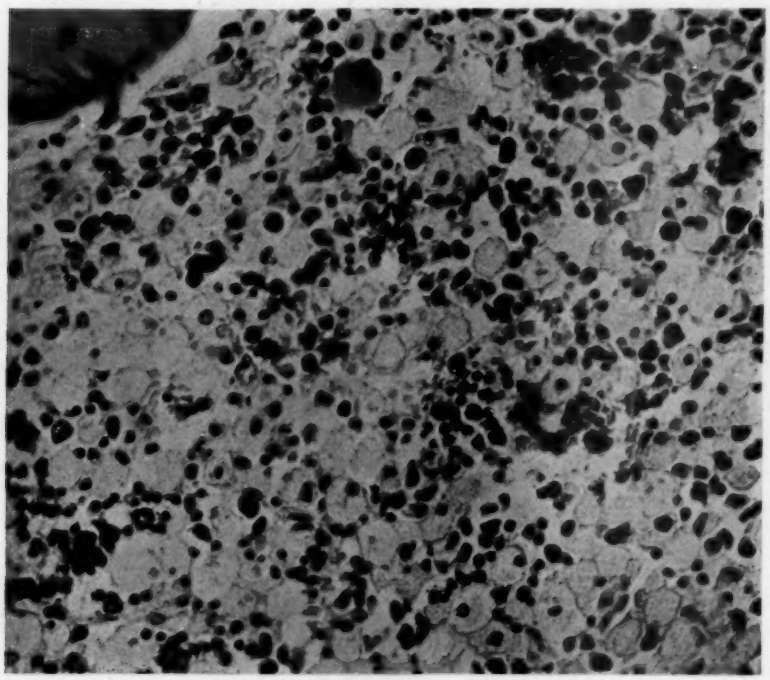


Fig. 3.—Section of bone-marrow; hematoxylin-eosin stain.

inferences regarding the partition of these fragments among the complex lipoids (neutral fat, lecithin, waxes, cerebrosides) as they occur in the living cell. The anatomist and histologist are mainly interested in the partition of these complex lipoids with their specific solubility in various solvents, their staining properties and their physiologic significance.

Extraction without preceding hydrolysis, although it will hardly accomplish a total exhaustion of the lipoids, is generally used for such investigations. We adopted a method for extraction which would afford a picture of the distribution of the lipoids with as little alteration of the in vivo state as possible.

The material may be fresh, formaldehyde-fixed or dried. Dry material is more easily extracted by such solvents as ether and chloroform, but there is always danger of partial hydrolysis and other autolytic processes during drying. The disadvantages of fixed material, e. g., hydrolysis due to the treatment with formaldehyde, have been pointed out by Pick [2] and recently by Weil.[3] The solvents best adapted for the extraction of fresh organs are acetone and alcohol. The

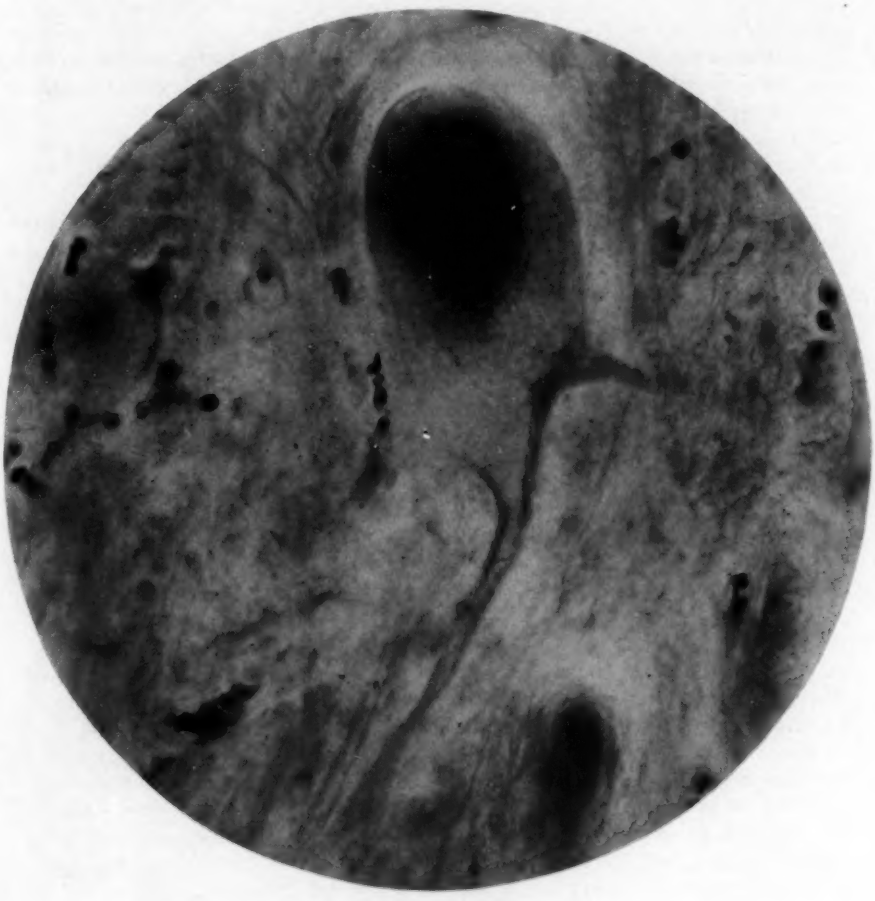


Fig. 4.—Section of brain; silver impregnation.

main disadvantage of the extraction of "fresh" tissue is the dilution of the solvent with the aqueous juice of the tissue; thus, the first extract contains some non-lipoidic material relatively high in nitrogen. This treatment, however, effects an immediate inactivation of the enzymes and also prevents destructive oxidation of unsaturated compounds.

2. Pick, L.: Ergebn. d. inn. Med. u. Kinderh. **29**:519, 1926.
3. Weil, A.: J. Biol. Chem. **83**:601, 1929.

We chose acetone for the first extractions; these extracts were evaporated to dryness and taken up with hot absolute alcohol. The alcohol-insoluble residue of the acetone fraction was excluded from the computation as consisting of nonlipoidic material. The material extracted by acetone and soluble in hot alcohol was assumed to contain all the neutral glycerides and most of the cholesterol. The phosphorus found was calculated as lecithin. Pure lecithin is rather insoluble in acetone, but its solubility in water, as well as in organic solvents, varies greatly, depending on the presence of concomitant substances. Some of the phosphorus content of the acetone fractions has to be attributed to lysolecithins or other degradation products of lecithin. The nitrogen content of these fractions is partly due to the phosphatids, the greater part to accompanying nonlipoidic substances of smaller molecular weight and high nitrogen percentage.

The acetone extraction was followed by three extractions with ether. These extracts contained most of the lecithin and some cephalin and cerebrosides. The residue was finally extracted by boiling absolute alcohol for cerebrosides and sphingomyelin. The combined ether and alcohol extracts were evaporated and digested with small amounts of cold ether. Although the supernatant portion was somewhat high in nitrogen, its phosphorus percentage suggested a lecithin content of 90 per cent and more. These fractions were designated "lecithin fractions." The residue was dissolved in warm ether and precipitated with acetone; the white precipitate was designated "fraction 1." The supernatant portion was brought to dryness, taken up in ether and again precipitated with acetone; this process was repeated two or three times, resulting in the isolation of the "fractions 2, 3 and 4" and mother liquor "ML." These, in the order in which they were precipitated, contained decreasing amounts of cerebrosides and increasing amounts of lecithin. The mother liquor contained appreciable quantities of combined and free cholesterol. The cephalin, because of its lower solubility, accompanied the cerebrosides and probably accounted for a large share of the phosphorus in the less acetone soluble fractions. While both cerebrosides and mono-aminophosphatides (lecithin and cephalin) contain only 2 per cent nitrogen, the diaminophosphatides (sphingomyelin) are about twice as rich in nitrogen. Their presence was partly responsible for the high nitrogen in some of these fractions. We did not attempt to isolate any of these lipoids in pure form because of the small amounts of starting material and because even the isolation of minute amounts of a pure substance would be without significance for the partition of the total lipoids.

The dry residues of the various fractions were made up to approximately 1 per cent solutions in alcohol or methyl alcohol-chloroform. These solutions were analyzed for phosphorus by a modification of the method of Kuttner and Cohen,[4] for nitrogen by macro-Kjeldahl and micro-Kjeldahl methods, for cholesterol by Bloor's method and for combined cholesterol likewise by Bloor's method after removal of the free cholesterol by digitonin. Every analysis was carried out in duplicate. The analytic results cannot be given in detail because of lack of space. It should be noted that after deduction of phosphatides and cholesterol and after allowing for the fatty acid combined with cholesterol, the balance of the acetone-soluble fraction was considered neutral fat; the undetermined portion of the other fractions, cerebrosides. The "fractions 1" containing the largest amounts of cerebrosides were analyzed polariscopically for kerasin. The specific rotation in approximately 1 per cent solutions in chloroform-methyl alcohol (3:1) was for the spleen +6.7 degrees, for the liver +6.8 degrees and for the brain +7.8 degrees. Phrenosin and sphingomyelin have a specific rotation of from +7 to

4. Kuttner, T., and Cohen, H. R.: J. Biol. Chem. **75**:516, 1927.

+8 degrees, under these conditions, and the values for lecithin and cephalin are of the same range, while kerasin exhibits a rotation of —5 degrees. Thus the presence of significant amounts of kerasin in our material was excluded. Small anisotropic spheroliths were obtained from these fractions, but they were too minute for Rosenheim's [5] test with the selenite plate.

Our results are summarized in table 1. The control organs were obtained from autopsies on children in the same age group. The results of all available analyses of the lipoids of the spleen and liver in cases of Niemann-Pick's disease on record are presented in figure 5. They are given as percentages of fresh organ. The cases of Wahl and Richardson [6] and Siegmund [7] were diagnosed as morbus Gaucher, but Bloom and Kern [8] and Pick [2] emphasized the true nature of these cases as that of morbus Niemann-Pick.

TABLE 1.—*Distribution of Lipoid in Case of Niemann-Pick's Disease and in Controls*

Organ	Weight of Portion Total Weight, Gm.	Weight of Portion Analyzed, Gm.	Total Solids, %	Extracted Lipoids, Percentage Wet Organ	Extracted Lipoids, Percentage Total Solids	Percentage of Total Lipoids Neutral Fat	Free Cholesterol	Cholesterol Esters	Phosphatides	Cerebrosides	Ratio N:P	Ratio Free to Total Cholesterol
Brain	630	273	17.0	7.75	45.6	None	3.35	25.55	53.5	17.6	1.37	0.18
Liver	500	310	26.4	12.1	45.8	0.3	4.9	11.25	67.9	15.65	1.03	0.42
Spleen	180	105	25.8	8.6	33.4	1.25	9.6	6.85	62.6	19.7	1.23	0.70
						Total Cholesterol						
Two livers (controls)	208	27.1		6.35	23.3	25.25	6.25	.....	(39.1)*	(29.4)*	1.3	(0.79)†
Three spleens (controls)	45	20.9		2.22	13.55	26.5	11.0	.....	41.5	21.0	3.2	(0.91)†
Brain												(0.65)†

* Approximation.
† From Beumer.[11]

TABLE 2.—*Results of Analysis of Spleen and Liver in Nieman-Pick's Disease and Controls, According to Wahl and Richardson*

	Total Lipoids, per Cent	Neutral Fat, per Cent
Normal spleens	20.5 to 21.8	9 to 14.6
Niemann-Pick spleen	52 to 54	1.3
Normal livers	23 to 27.8	12.2 to 19
Niemann-Pick liver	37.2	2.8

The case of Wahl and Richardson was not incorporated in figure 5, because these investigators refer their figures to dry material and classify the lipoids in a somewhat different manner. Their percentages for the total lipoids and neutral fat of dry material are given in table 2.

5. Rosenheim, O.: Biochem. J. **8**:110, 1914.

6. Wahl, H. R., and Richardson, M. L.: A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant, Arch. Int. Med. **17**:238, 1916.

7. Siegmund, H.: Verhandl. d. deutsch. path. Gesellsch. **18**:59, 1921.

8. Bloom, W., and Kern, R.: Spleens from Gaucher's Disease and Lipoid-Histiocytosis: Chemical Analysis, Arch. Int. Med. **39**:465, 1927.

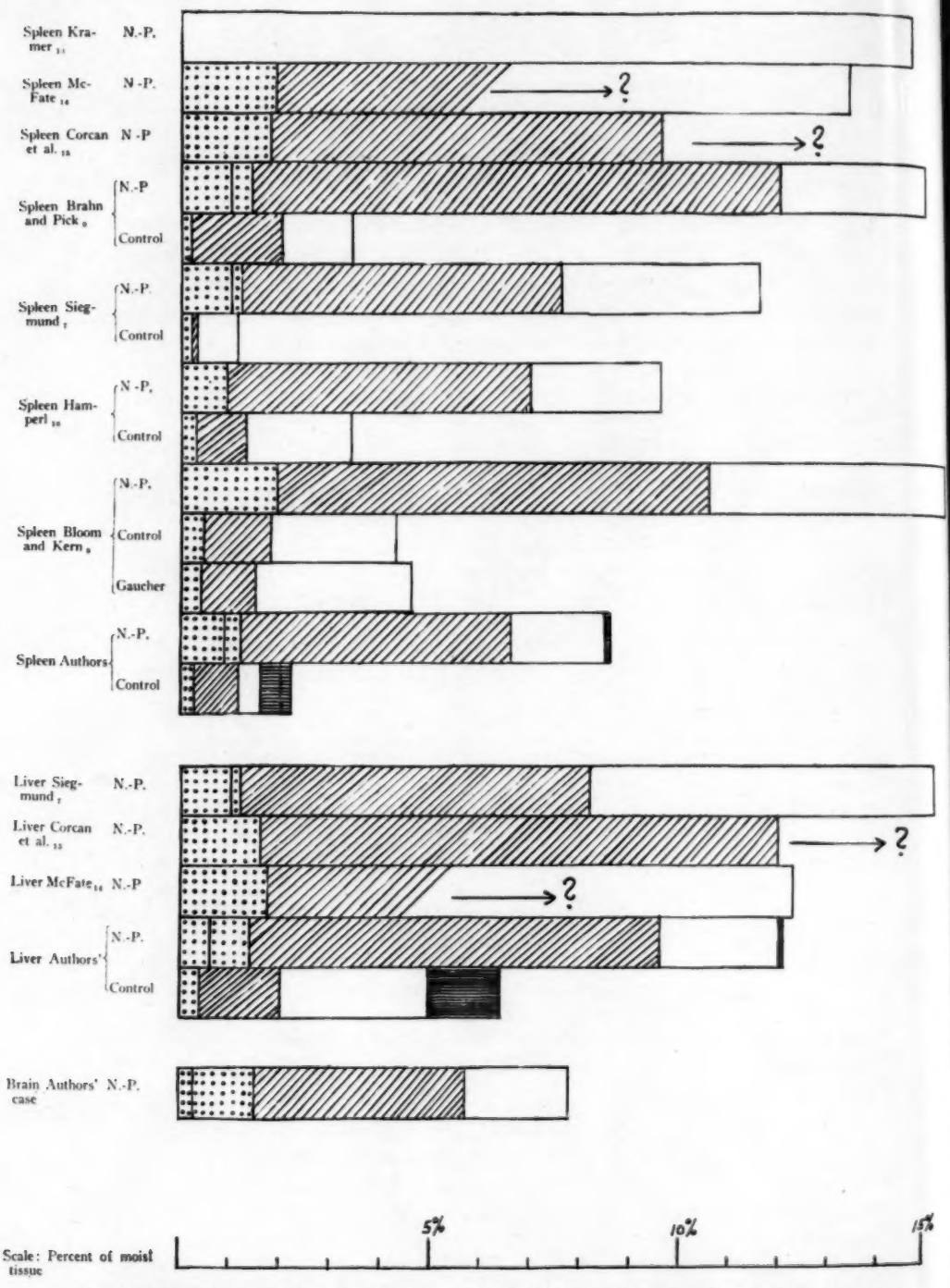


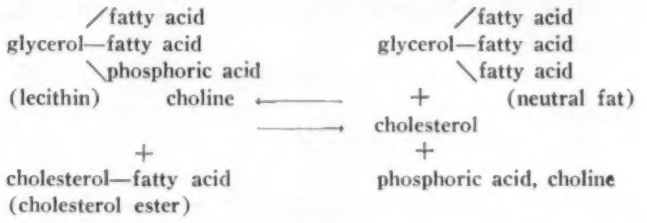
Fig. 5.—Distribution of lipoid in Niemann-Pick's disease as compared with that in controls, according to various authors. The dotted space represents free and combined cholesterol (if not subdivided, total cholesterol); the diagonally ruled space, phosphatides; the horizontally ruled space, neutral fat, and the blank space, cerebrosides or undetermined lipoids. The values are given as percentages.

These figures for neutral fat obtained by a different procedure are in agreement with our own. The depletion of fat has been observed clinically as general emaciation, pathologically by Pick [9] and chemically by Wahl and Richardson and by ourselves in the present analysis. The disappearance of neutral fat is the most striking chemical feature of Niemann-Pick's disease.

The increase in lipoid phosphorus was observed in every analysis on record. It may be interpreted as an increase of lecithin or mono-amino-phosphatides in general, but the question as to what part of the increase is due to sphingomyelin and other phosphatides (Epstein [10]) is left for further investigation. The relative increase in cholesterol is smaller, but comparable to that of the phosphatides. The proportion of free cholesterol in total cholesterol was 18 per cent in the brain, 42 per cent in the liver and 70 per cent in the spleen. Brahn and Pick [9] found 71 per cent in the spleen; Siegmund,[7] as much as 85 per cent in the spleen and 82 per cent in the liver.

Our figures are considerably lower than those given for normal children by Beumer,[11] who found in an 8 months old child that of the total cholesterol in brain, liver and spleen, 65 per cent, 79 per cent and 91 per cent, respectively, was free cholesterol. Brahn and Pick, however, found only 51 per cent in a normal spleen.

This increase of both phosphatides and cholesterol esters and the failure of the organs to store or to retain neutral fat suggests the following explanation: An equilibrium obtains normally between



This equilibrium governs the transport, utilization and deposition of fat. It is disturbed in Niemann-Pick's disease perhaps by a failure of the enzymatic apparatus—with the effect that the lipoid partition in the organs is shifted to the left side of the foregoing equation.[12]

The analysis of the brain was undertaken with the hope that light might be thrown on the etiologic relationship between Niemann-Pick's and Tay-Sachs' disease. According to Pick, the histologic changes are

9. Brahn, B., and Pick, L.: Klin. Wchnschr. **6**:2367, 1927.

10. Epstein, Emil: Virchows Arch. f. path. Anat. **274**:294, 1929.

11. Beumer, H.: Monatschr. f. Kinderh. **19**:409, 1921.

12. Sobotka, H.: Ueber Umesterungen im Lipoidstoffwechsel, Naturwissenschaften **18**:619, 1930.

practically the same whether the degeneration of lipoid occurs in the liver, spleen, spinal cord or brain. Bernard Sachs, in discussing the clinical picture in the present case, stated: "The resemblance is so great in these diseases that there can be little doubt that they are allied. The Niemann-Pick type seems to represent the wide-spread lipoid degeneration and amaurotic family idiocy the same degeneration limited to the central nervous system."

In the study of this brain, no neutral fat was found. High percentages of phosphatides and cholesterol, particularly combined cholesterol, were encountered here as in the other organs; this seems less significant, however, because of the relatively high concentrations of these lipoids in normal brains.[13] It would be desirable to compare the present observations with those obtainable by analysis of the organs in instances of amaurotic family idiocy without hepatosplenomegaly.

The chemical data that clearly differentiate the present case from Gaucher's disease are: the absence of relative increases of cerebrosides, corroborated by the low nitrogen-phosphorus ratio, and the absence of unusual amounts of kerasin, proved by the dextrorotation of the fractions involved.

We urge pathologists who contemplate analyses of the lipoids of organs in cases of Niemann-Pick's disease, family idiocy, Christian's disease and related conditions not to fix the material with formaldehyde, but to place the minced or chopped material without delay under acetone. The material might be kept in this state until its chemical analysis, including that of the acetone supernatant portion, proves convenient.

SUMMARY

The analysis of the lipoids of spleen, liver and brain in a case of lipoid histiocytosis (Niemann-Pick) associated with amaurotic family idiocy showed: (1) the disappearance of neutral fat; (2) considerable increase of phosphatides and cholesterol, particularly cholesterol ester, and (3) the absence of kerasin.

13. Peritz, G., in Oppenheimer: Handbuch der Biochemie, Jena, Gustav Fischer, 1925, vol. 4, p. 360.

ACTINOMYCOSIS OF THE HEART

REPORT OF A CASE WITH ACTINOMYCOTIC EMBOLI *

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Since Israël [1] reported the first cases of actinomycosis in man in 1878, a great number of reports have appeared in the literature. A report of a single case is warranted only if the case shows unusual features. We believe that the case here described is atypical both in regard to the distribution of the lesions and in regard to their gross anatomic characteristics. The most important mode of propagation of *Actinomyces* in the body is by continuity of growth and infiltration similar to those of malignant neoplasms, particularly since it does not respect anatomic boundaries and normal capsules. Metastasis through lymphatic channels is extremely rare. As a rule, regional lymph nodes may be found enlarged, but not involved by the specific organism. In the literature we found only one report of metastatic involvement of lymph glands (von Baracz [2]). Hematogenous metastasis is more frequent, although far from common. Local lesions at any place may break into the circulatory system and so give rise to hematogenous propagation. Relatively few reports of such cases could be found in the literature. Israël did not mention the site of the invasion of the vascular system; the same is true of Abée;[3] but in both their cases there was definite evidence of hematogenous spread. Invasion of the blood stream occurred in: (1) the myocardium in the cases of König,[4] Münch,[5] Paltauf,[6] Lutz [7] and Paetzold; [8] (2) the vena cava in the cases

* Submitted for publication, May 26, 1930.

* From the Department of Pathology, Herman Kiefer Hospital, Detroit, and the William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Mich.

1. Israël, J.: Virchows Arch. f. path. Anat. **74**:15, 1878.
2. von Baracz, R.: Arch. f. klin. Chir. **68**:1050, 1902.
3. Abée, C.: Beitr. z. path. Anat. u. allg. Path. **22**:162, 1897.
4. König, A.: Inaugural Dissertation, Berlin, 1884.
5. Münch, A.: Cor.-Bl. f. schweiz. Aerzte **18**:234, 1888.
6. Paltauf, R.: Wien. klin. Wchnschr. **3**:487, 1890.
7. Lutz, R.: Inaugural Dissertation, Munich, 1910.
8. Paetzold, P.: Frankfurt. Ztschr. f. Path. **16**:415, 1915.

of Hanau [9] and Adler; [10] (3) a large hepatic vein in a case of Benda [11] and (4) the coronary artery and the right ventricle in the second case reported by Benda. In a number of other cases the reports of which we have studied vascular invasion may have occurred, but the descriptions are not always definite enough to warrant a conclusion. Additional cases have quite likely escaped our notice.

Kaufmann [12] emphasized the fact that actinomycotic involvement of the heart and pericardium is rare. In the accompanying table are summarized some of the larger statistics, showing the incidence of pericardial and myocardial involvement

In a series of about 470 cases of actinomycosis, the incidence of pericardial and myocardial involvement was less than 2 per cent. Thirty-two years after Israël's first description of the disease, Lutz was able

Incidence of Pericardial and Myocardial Involvement in Cases of Actinomycosis

Author	Cases of Actinomycosis	Cases Showing Involvement of: Pericardium	Myocardium
Bostroem (Beitr. z. path. Anat. u. allg. Path. 9: 1, 1891)	12	0	0
Schlange (Arch. f. klin. Chir. 44: 863, 1892)	120–130	0	0
Ruhräh (Ann. Surg. 30: 417, 605 and 722, 1899; 31: 235, 1900)	72	0	0
Shiota (Deutsche Ztschr. f. Chir. 101: 289, 1901)	55	1	0
Baracz [2]	63	0	1
Heinzelmann (Beitr. z. klin. Chir. 39: 526, 1903)	56	1	0
Harbitz and Gröndahl (Beitr. z. path. Anat. u. allg. Path. 50: 193, 1911)	37	4	4
Total	465–475	6	5

to collect but twelve cases of involvement of the myocardium, and he added one. He did not mention a case published by Paltauf in 1890 and one described by Abée in 1897. Since that time, the following cases have come to our notice: one case of actinomycotic pericarditis and myocarditis, one case of incipient actinomycotic abscess in the myocardium, one which showed in addition to an acute serofibrinous pericarditis actinomycotic lesions in the endocardium and one with a purulent infiltration of the pericardium and an abscess in the heart—all described by Harbitz and Gröndahl,[13] and one case of generalized actinomycosis in which an adhesive pericarditis and multiple nodules in the myocardium were found, reported by Paetzold.

9. Hanau, A.: Cor.-Bl. f. schweiz. Aerzte **19**:165, 1889.

10. Adler: Deutsche med. Wchnschr. **16**:596, 1890.

11. Benda, C.: Deutsche med. Wchnschr. **26**:70, 1900.

12. Kaufmann, E.: Spezielle pathologische Anatomie, ed. 8, Berlin, W. de Gruyter & Company, 1922.

13. Harbitz, F., and Gröndahl, N. B.: Beitr. z. path. Anat. u. allg. Path. **50**: 193, 1911.

Involvement of the lung is a frequent occurrence, either as an apparently primary invasion or as a secondary extension by direct contact from lesions of the upper part of the respiratory tract, from abdominal foci, from preexisting pericarditis or from infections of the wall of the chest. Embolic involvement is apparently rare, even in cases with myocardial lesions. True embolic pulmonary involvements resulting in multiple hemorrhagic infarctions were reported by Paltauf, Benda and Lutz. Paltauf's case resembled our case more than any of the others found described in the literature. The description of his case in brief, is as follows:

> The lungs contain metastatic abscesses and hemorrhagic infarctions; the pleura over these lesions shows fresh fibrinous exudations. The branches of the pulmonary artery within these foci are filled with pus. The pericardium contained 300 cc. of thick pus which contained the characteristic sulphur granules. In the anterior wall of the right ventricle, there was an actinomycotic abscess, measuring 3 × 1½ cm., extending with small pedunculated granulations into the endocardium which was slightly ulcerated.

REPORT OF CASE

History.—R. R., a white man, aged 30, a coal miner, was admitted to the Tuberculosis Division of the Herman Kiefer Hospital on June 14, 1929, complaining of cough, pain in the chest, swelling of the legs, occasional night sweats and loss of weight. His illness began seven months previous to his admission with general malaise and cough. About two months later, he suffered from an acute pain in the chest across the upper sternal region. Because of weakness he had to give up work and go to bed; but he had no medical care until six weeks prior to admission; then he applied at a clinic for medical aid. At that time, he felt a heaviness in his legs and arms. Edema of the extremities was noticed at night. There were pain and swelling in the right arm and right thigh.

Drainage of the gallbladder was performed in 1923 and cholecystectomy in 1928. Otherwise, the history was of no interest. The family history bore no relation to the patient's illness.

Physical Examination.—On admission, marked dulness was present over the base of the right lung. No rāles were heard. The pulse rate was 132. The abdomen was greatly distended with fluid, particularly the right side, which bulged. An old laparotomy scar was present on the right side of the abdomen. Both lower extremities and the right hand were edematous. A brawny induration was present in the lateral and posterior portion of the middle of the right arm. A similar induration was present in the right thigh. The scrotum was greatly enlarged and edematous.

Laboratory Examination.—Slight secondary anemia was found. The total white count was 19,600, with 82 per cent polymorphonuclears and 18 per cent lymphocytes. On June 18, the white cell count rose to 26,600, with 86 per cent polymorphonuclears and 14 per cent lymphocytes. Three examinations of sputum were negative for tubercle bacilli. The results of urinalysis were negative, except for occasional red blood cells.

Roentgen examination on June 18, 1929, showed thickening of the pleura on the right side and evidence of effusion. There was no mottling of the right lung to suggest tuberculosis. The left lung was normal. The heart was also normal.

Diagnostic puncture of the right pleural cavity revealed the presence of clear, straw-colored fluid. Cultures of this fluid remained sterile. No acid-fast bacilli or other bacteria could be found on smears. Inoculations of guinea-pigs gave negative results for tuberculosis.

Abdominal fluid examined for bacteria was negative. Inoculations of animals gave negative results for tubercle bacilli.

Clinical Course.—The temperature was irregular, ranging from 97.8 tc 100.8 F., being 95 F. shortly before death. The pulse rate varied between 80 and 140 per minute. The rate of respiration was between 16 and 32 per minute; immediately before death, it was 48. Two days before death, the swelling in the arm and thigh broke down, and the purulent discharge was moderately profuse. On the morning of July 4, breathing became labored and the pulse weak and irregular. The pulse continued to be irregular until July 13 and was thready immediately before death on this day. Profuse clammy perspiration occurred on the day preceding, and dyspnea became marked several hours before, death.

Necropsy.—A necropsy was made thirty-eight hours after death, but permission to open the skull was not granted. A description of the major lesions follows:

On the posterior aspect of the upper third of the right arm was an induration of the subcutaneous tissues. In the skin over this swelling several openings were present. The largest of these openings was 5 mm. in diameter, and through it much thick, greenish-yellow purulent material could be expressed from the deeper part of the induration. A similar induration was present in the lateral portion of the right thigh. Around the several small openings in the skin over this swelling granulation tissue was present, and the amount of pus that could be expressed was much less than in the arm.

Both pleural cavities contained turbid, yellowish-gray fluid in which were suspended particles of fibrin. The right cavity contained approximately 1,200 cc. and the left about 900 cc. The parietal pleura on each side was greatly thickened and fibrous.

The pericardial cavity was almost completely obliterated by fibrous adhesions. The parietal pericardium was thickened and contained small yellow foci, especially at the apex of the heart, where it was firmly adherent to the epicardium. Both ventricular walls at this site were softened by a deposit of white fibrous tissue in which were many small, soft foci, containing a yellow purulent substance (fig. 1). These foci resembling abscesses measured approximately 3 mm. in diameter. There was no apparent rupture into the chambers of the heart, although the inflammatory process involved almost the entire thickness of the ventricular walls. The apex of the heart was rounded, owing to the increase in the fibrous tissue, the enlargement being external. Where not involved, the myocardium was dull red and very moist. It showed some cloudiness. The ring of the mitral valve was enlarged, and its leaflets did not close the orifice completely. At the bases of the leaflets, slight sclerosis was noted, while their free margins were thin and smooth. The leaflets of the tricuspid valve showed wrinkled margins, but no ulceration or vegetation. Small lipoid deposits were present on the surfaces of the cusps of the aortic and pulmonary valves. The volume of the left auricle was approximately twice that of the right, and both contained freshly clotted dark blood, as well as pale clots with much fibrin.

The right lung was completely devoid of air and was of a soggy, beefy consistency. The left lung contained few areas which were crepitant. Both organs

were covered with dark, bluish-black pleurae in which were several patches of white fibrous tissue, particularly near the bases and over the lower anterior part of the upper lobe of the left lung.

On section, both lungs were of an even, almost black color. The large trunks near the hili were surrounded by rather dense fibrous tissue. Scattered

Fig. 1.—The left ventricle of the heart bisected near the apex, showing fibrosis of the wall with small pockets containing yellow purulent material. Several of these pockets are empty. A portion of the parietal pericardium at the left shows thickening and a rough inner surface. The wall of the left auricle is greatly thickened because of fibrosis.

irregularly throughout the lungs were many foci of hard tissue. The majority of these were wedge-shaped with the broad bases lying directly below the pleura, but a few smaller round ones were seen more centrally located. What were appar-

ently the most recent lesions showed densely infiltrated hard tissue markedly protruding above the cut surface of the uninvolved pulmonary tissue. They were dark purple and were surrounded by less densely infiltrated and somewhat paler zones. The less recent lesions were not so elevated, but hard. They showed dark red cut surfaces, mottled with yellow. What appeared to be the oldest lesions showed central softening. These were dirty gray.

Fig. 2.—A section from a hemorrhagic focus in the lung showing a mass of Actinomyces surrounded by polymorphonuclear leukocytes. External to the abscess is a large accumulation of blood.

In the lateral portion of the upper lobe of the right lung was a grayish-yellow, hard, round, encapsulated subpleural nodule. (Primary focus?)

The terminal portion of the ileum contained several transverse scars in Peyer's patches. Small nodules were present in the midportions of these scars. The wall of the ileum over these areas was thickened. Several mesenteric lymph nodes were hard and contained cheesy material, with deposits of small amounts of calcium.

Histologic Examination.—A section taken from the peripheral part of the left ventricle of the heart showed the epicardium to be replaced by granulation tissue with numerous newly formed capillaries. In this tissue were scattered collections of lymphocytes and plasma cells. In the myocardium under the granulation tissue were foci consisting almost entirely of polymorphonuclear leukocytes. These leukocytes replaced the myocardial fibers. Dense connective tissue separated this leukocytic exudate from the bundles of myocardial fibers bordering the zone of

Fig. 3.—A branch of the pulmonary artery containing Actinomyces with a mass of leukocytes.

inflammation. A few muscle fibers surrounded by the connective tissue showed degeneration. At the centers of several of the foci of polymorphonuclear leukocytes were masses of *Actinomyces* in characteristic arrangement.

One section of lung showed a large hemorrhage involving a number of alveoli, in the middle of which were several foci of neutrophilic polymorphonuclear leukocytes. At the centers of these purulent foci were masses of *Actinomyces* (fig. 2). The alveoli bordering the hemorrhagic area showed congestion of capillaries, and there was a slight extravasation of red cells into the air spaces of a few of them.

Several other sections showed large collections of leukocytes at the periphery of the lung immediately under the pleura. These foci were sharply demarcated from the adjacent normal alveoli. In them were masses of the ray fungus. On the pleural sides of these infarct-like areas, connective tissue was present in moderately thick layers.

Another type of lesion consisted of a leukocytic accumulation at the center of which *Actinomyces* was present. Surrounding the collection of leukocytes was

Fig. 4.—A vein in the ileum containing Actinomyces and much pus. The surrounding structures of the submucosa are free from any reaction.

a capsule composed of dense hyaline connective tissue. External to this capsule was granulation tissue containing numerous capillaries and scattered lymphocytes. The alveoli immediately adjacent to the area of inflammatory reaction was normal in appearance.

In one section (fig. 3), a colony of *Actinomyces* was seen in a branch of the pulmonary artery, leaving no doubt as to the etiologic nature of the infarction.

Carbon pigment was present in large amounts throughout the parenchyma of the lung in all sections studied.

In the submucosa of the ileum were two areas of inflammation characterized by lymphocytic infiltration between proliferating fibroblasts. One of these areas was around an artery that contained an organized thrombus obliterating its lumen. The other was adjacent to a vessel that was filled with polymorphonuclear leukocytes and contained *Actinomyces* (fig. 4). The mucosa of the ileum was intact, except in the region of the thrombosed vessel, where it was denuded and a fibrosed base of the ulcer was exposed.

A section from skeletal muscle of the arm showed extensive perivascular accumulations of lymphocytes and plasma cells. Abscesses consisting of polymorphonuclear leukocytes and surrounded by walls of dense hyaline connective tissue were noted in several bundles of muscle fibers. The adjacent muscle was diffusely invaded by connective tissue. Many of the muscle fibers in this mass showed necrosis; one area showed coagulation necrosis.

A section of skeletal muscle from the thigh showed essentially the same type of inflammation. Masses of ray fungus were found in several of the abscesses.

The intima and media of the aorta were normal. In the adventitia, scars and granulation tissue were seen. Collections of lymphocytes and plasma cells were present around several arterioles. An occasional abscess was observed and one contained *Actinomyces*.

The liver showed marked passive congestion.

The spleen showed passive congestion. Branches of the splenic artery showed hyaline thickening.

The kidneys presented passive congestion and cloudy swelling of the tubular epithelium.

Diagnosis.—The essential points of the pathologico-anatomic diagnosis were as follows: induration, with central abscess formation and multiple draining sinuses on the right arm and right thigh; bilateral fibrinopurulent pleuritis; bilateral fibrotic pleuritis of parietal pleura; obliterative pericarditis; multiple abscesses in pericardium; myocardial abscess; multiple hemorrhagic infarcts in both lungs; ascites and multiple abscesses in the mucosa of the ileum.

COMMENT

As mentioned, the case reported is unusual both in the distribution of foci and in the gross appearance of the latter. The portal of entry could not be determined. The teeth were noted as showing caries, but there were no mucosal lesions in the mouth. The lung did not contain any foci the structure of which suggested a relatively old lesion; in fact, the pulmonary lesions, showing rather fresh hemorrhage and no development of fibrous tissue, were most likely of recent development. The subcutaneous abscesses, which were surrounded by more or less marked fibrous interstitial myositis, were undoubtedly considerably older than the pulmonary foci or the intestinal lesions, which were free from fibrosis. Structurally, the myocardial, pericardial and peripheral lesions were the oldest. The myocardial and pericardial lesions cannot possibly be considered to have been primary, and if the peripheral lesions are considered primary, one has to assume two widely separated portals of entry, an unsatisfactory solution.

All that can be said is that the myocardium or pericardium became invaded presumably by way of the blood stream, since no lesions were seen that might have infected these structures by continuous progression. From the myocardial focus, spread must have occurred both by the systemic and by the pulmonary circulations, as attested by recent (endovascular) lesions in the ileum and in the wall of the aorta and by the multiple embolic foci in the lungs. As in the case of other infectious emboli, why certain organs were infected and why others (notably the spleen and the kidneys) escaped remains unexplained.

There was nothing in the gross appearance of the various lesions to suggest actinomycotic infection. The various abscesses looked like products of nonspecific, subacute purulence. The exudate was purulent, containing none of the "sulphur granules"; the same is true of the pleural effusion. In all regards, the pulmonary lesions had the characteristics of recent hemorrhagic infarcts.

SUMMARY

A case of embolic actinomycosis with multiple endovascular metastases is reported.

THE OCCURRENCE AND NATURE OF SPONTANEOUS ARTERIOSCLEROSIS AND NEPHRITIS IN THE RABBIT*

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From the clinical and pathologic standpoints, the study of arteriosclerosis and nephritis is most important. These conditions have much to do with efficiency during life. Arteriosclerosis is responsible for the death of many persons beyond middle age. In a study of 9,149, necropsies performed at the Krankenhaus Charité in Berlin during a period of eight years, Hesse[1] determined that it is the cause of 10.2 per cent of all deaths in persons over 40 years of age. From reports issued by the U. S. Public Health Service we have estimated that of persons of 45 years of age or beyond, 45.5 per cent will die from one of the triad of cardiovascular-renal diseases. In this group, arteriosclerosis is a most prominent pathologic observation. Although much investigative work has been done and much has been written concerning the etiology of these diseases, few basic facts have been proved. The field is a fertile one for investigation.

Experimentation on animals is essential in reaching a solution of the problems related to the etiology of arteriosclerosis and nephritis. Of the various laboratory animals, the rabbit is, and probably will continue to be, the one most used. The rabbit has been maligned as an experimental animal on the ground that it is subject to spontaneous changes that make any experimentally produced alterations difficult of interpretation. This is particularly true of the spontaneous occurrence of arteriosclerosis, concerning the incidence of which there is the greatest variance in the relatively few reports available, ranging from 0 per cent to 34 per cent.

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* From the Laboratories of the Cottage Hospital.

1. Hesse, M.: Zur Statistik der Atherosklerosesterblichkeit, Frankfurt. Ztschr. f. Path. **35**:477, 1927.

The literature on this subject has been summarized by Newburgh and Clarkson,[2] who stated that Steinbliss found no sclerosis in the examination of the aortas of more than 500 rabbits. Loeb had the same result in 483 "normal" rabbits. Rosenow, examining 1,548 rabbits, found arteriosclerosis in only 3, while in a later series of 300, he found none. "Miles, on the other hand, found aortic lesions in 17 of 49 (34.6 per cent) of supposedly normal rabbits, with primary involvement of the media." Levin and Larkin found spontaneous atherosclerosis in 13 per cent of rabbits, but these animals had been used for experimental purposes the exact nature of which is not clear. Of Newburgh and Clarkson's series of 116 rabbits, some of which had been used as controls for their experiments, and the others for the demonstration of the action of drugs and for the obtaining of blood serum, only 4 (3.4 per cent) showed changes in the aortas. Grossly, there were small intimal papules of the ascending and transverse portions of the aortic arch. Microscopically, the intima was normal, but there was necrosis or calcification of the medial muscle cells. True intimal sclerosis was not found in a single animal of this group.

It is evident that in addition to wide variation in the reported incidence of arteriosclerosis, there has frequently been the failure to make a careful microscopic study.

ARTERIOSCLEROSIS

We have examined the blood vessels and kidneys of approximately 190 rabbits living the year round in outdoor hutches. These animals were raised from our own stock, and their age at death varied from 2 to 3 years. For the most part, they had been used in the standardization of insulin and as control animals in various experiments. Their diet consisted of barley, 52. Gm., and alfalfa, 150 Gm., daily.

Two types of sclerosis of the large vessels were found. One consisted grossly of a gray depression of the intima, and was found 11 times, or in 5.8 per cent; the other, a yellow elevated lesion of the intima, occurred in 6 instances, or in 3.1 per cent.

Grossly, the appearance of the depressed type of sclerosis is as follows: There are many shallow pits or depressions of the inner surface of the aorta, which are gray, circular and vary from 1 to 3 mm. in diameter. They are limited for the most part to the arch of the aorta, and are scattered diffusely, lacking the tendency of intimal arteriosclerotic plaques to be grouped about the ostia of the intercostal arteries. Over the edge of these depressions, the intima itself is folded, but otherwise unaltered. Some of the lesions are almost umbilicated,

2. Newburgh, L. H., and Clarkson, S.: The Production of Atherosclerosis in Rabbits by Feeding Diets Rich in Meat, Arch. Int. Med. **31**:653, 1923.

the circular edges projecting slightly above the surface of the aorta when it is held out flat. When the aorta is held up to the light, pronounced thinning at the bases of the depressions is evidenced by the increased transmission of light through them.

As seen in histologic sections including the base of a depression, the aortic wall is frequently thinned to one half of its normal thickness.

Fig. 1.—Early spontaneous intimal arteriosclerosis, showing subendothelial lipoid infiltration. Grossly, this lesion appears as a yellow papule.

The intima is thrown into irregular folds, but its histologic structure is unaltered. Groups of muscle cells well within the media may be but otherwise unaltered. Some of the lesions are almost umbilicated, partly or completely necrosed, or entirely replaced by calcium deposits extending in streaks from 1 to 2 mm. wide for some distance along the vessel wall. Beneath the intima may be scattered a few fat-laden cells between the muscle fibers, but they are strictly limited to the inner part

of the media. This type of arteriosclerosis, a calcification of the media, occurring in 5.8 per cent of our animals, had an entirely different histologic appearance from the second or intimal type.

In this intimal type, which involved most frequently the root and arch of the aorta, though commonly extending throughout its course down to the iliac bifurcation, raised yellow plaques are present, which

Fig. 2.—A more advanced stage of intimal arteriosclerosis. Note thickness of intima as compared with media.

vary from 1 mm. to 1 cm. in their greatest dimension. Early in the process they are discrete, and tend to be grouped about the mouths of the intercostal arteries, but in advanced instances they may become confluent and entirely cover the surface of the wall. In this group, such advanced changes were encountered only twice. Calcification of the plaques may occur, as evidenced by a gritty sensation when the knife is passed through them, but in our rabbits ulceration was not found.

The elasticity of the aorta is decreased in proportion to the degree of involvement of its wall.

The histologic picture depends on the degree of development of the lesion. Three processes are evident: degeneration, infiltration and regeneration, which may go hand in hand. Our histologic studies have demonstrated that the first change is a swelling of the intercellular cement substance directly beneath the endothelium. The tissue is

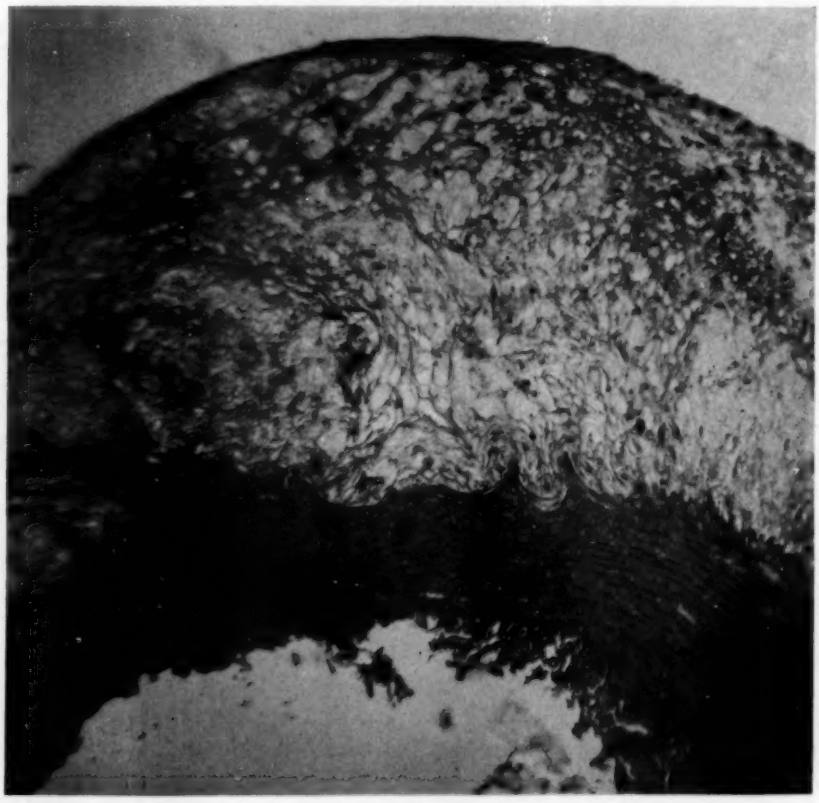

Fig. 3.—Far advanced intimal arteriosclerosis. The media is thinned, but otherwise unaltered.

edematous, and the connective tissue fibrils are pushed apart. Large fat-laden cells appear, coincident with a beginning necrosis of the connective tissue cells in this region, and are pushed toward the media by a connective tissue hyperplasia, which rapidly follows beneath the endothelium as the lesion progresses. At this stage, there is grossly evident a small yellow papule bulging slightly above the true level of the intima. Further necrosis of the subendothelial cells now takes place with replace-

ment by hyaline material and lipoid substances, as the process extends downward and lateralward. Spaces having the shape of cholesterol crystals may be seen in some regions just internal to the media, which have resulted from the solution of that substance during the preparation of the microscopic sections. The lesion may now measure twice the thickness of the rest of the arterial wall. Deposition of calcium may, and often does, occur. The internal elastic lamina is frayed and broken. Occasionally, the process extends by continuity into the superficial layers of the media, but only in advanced lesions. In most instances, the media beneath the lesion appears thinned, but otherwise unchanged.

In man, two types of sclerosis of the larger vessels have long been recognized. One involves only the intima. It consists of yellow or gray lesions that project into the lumen of the vessel and tend to be located near points of stress (i.e., about the mouths of the intercostal arteries, at the iliac bifurcation of the aorta, etc.) It affects arteries that are primarily of elastic structure, such as the aorta, the iliac and carotid arteries, and those of the brain. The media in this type of arteriosclerosis often escapes uninjured.

The second type of arteriosclerosis in man presents a different pathologic picture. Arteries in which muscular tissue is predominant, such as those supplying the abdominal organs and extremities, are affected by a necrosis of the media with secondary calcification, the lesions tending to be situated in ringlike fashion around the circumference of the vessel wall. This Monckeberg type is recognized clinically by the stiffened, beaded or "goose-neck" feel of the radial or dorsalis pedis artery to the palpating finger, and by the tortuosity and prominence of the brachial artery.

In the rabbit, differentiation of arterial structure into the elastic and muscular types is not so pronounced. Klotz,[3] in 1906, stated that the aorta of the rabbit is partly elastic, partly muscular in structure, and hence can develop both the intimal and medial types of arteriosclerosis. It was his opinion that the intimal type in the rabbit has its analog in man in arteriosclerosis of the arteries predominantly of elastic structure, and stressed the fact that the medial sclerosis of the rabbit is similar to the Monckeberg arteriosclerosis of man.

NEPHRITIS

Of this same group of 190 animals, 4, or 2.1 per cent, on histologic examination, revealed spontaneous nephritis. Between the spontaneous nephritis and the spontaneous arteriosclerosis, no relation seemed to exist,

3. Klotz, O.: A Discussion on the Classification and Experimental Production of Arteriosclerosis, Brit. M. J. **2**:1767, 1906.

as they did not occur in combination in a single instance in the 21 animals with lesions of the blood vessels and kidneys.

In addition to this series of 190 rabbits, we had a second series of 20 that were found to have spontaneous nephritis during life as determined by the repeated presence of albumin, cylindroids and casts in the urine on monthly examinations. These rabbits were selected from a group of 250 healthy animals in our hutches. Their average age at the time the nephritis was discovered was 6 months, and they were followed for a period of three years. They were fed 85 Gm. of barley and 50 Gm. of alfalfa daily, with the addition of greens twice each week. This diet proved to be so balanced that their urines were neutral or slightly alkaline in reaction, the p_H averaging 7. During the last year of the three year period, 10 of the 20 animals were placed on a liver diet suggested by McCollum,[4] to determine whether the pathologic alterations already present would be exaggerated by the feeding of a diet having a high content of protein. Acid urines with an average p_H of 6.2 were passed by these animals while fed this diet. Near the conclusion of the experiment, 12 of the animals died, 6 in the group fed alfalfa and barley and 6 in the group fed liver diet. At autopsy, pneumonia was present in 5 animals. One had died from a ruptured blood vessel following the passage of a stomach tube. In the remaining 6 animals, the cause of death was not evident. Death from uremia was a possible explanation. Obvious uremic symptoms had not been present, however.

The blood chemisty and the phthalein output of these animals were determined at the end of two years and at the conclusion of the experiment. The average of the nonprotein nitrogen for the 8 surviving animals had increased from 36.85 mg. per hundred cubic centimenters of blood to 49.73 mg., the urea nitrogen from 19.86 to 26.67 mg. and the phthalein percentage for one hour had decreased from 62.3 to 53.3 per cent.

These changes, together with the studies of the blood pressure made throughout the course of the experiment, will be reported in detail in a subsequent communication.

It must be recognized that the occasional presence of albumin and casts in the urine does not necessarily signify nephritis in rabbits, but when these are repeatedly present over long periods of time (in our animals, for a period of three years) and when accompanied by a demonstrable change in blood chemistry and decrease in function of the kidney, the presence of nephritis cannot be doubted. The results

4. Polvogt, L. M.; McCollum, E. V., and Simmonds, N.: The Production of Kidney Lesions in Rats by Diets Defective Only in that They Contained Excessive Amounts of Protein, Bull. Johns Hopkins Hosp. **34**:168, 1923.

of the histologic examination of the kidneys of these animals justify this conclusion.

In studying the alterations found in the arteries and kidneys of this group of 20 rabbits, in which a spontaneous and a persistent nephritis had been demonstrated by the aforementioned criteria, it is advisable to divide the group into two subgroups of 10 animals each. The first of

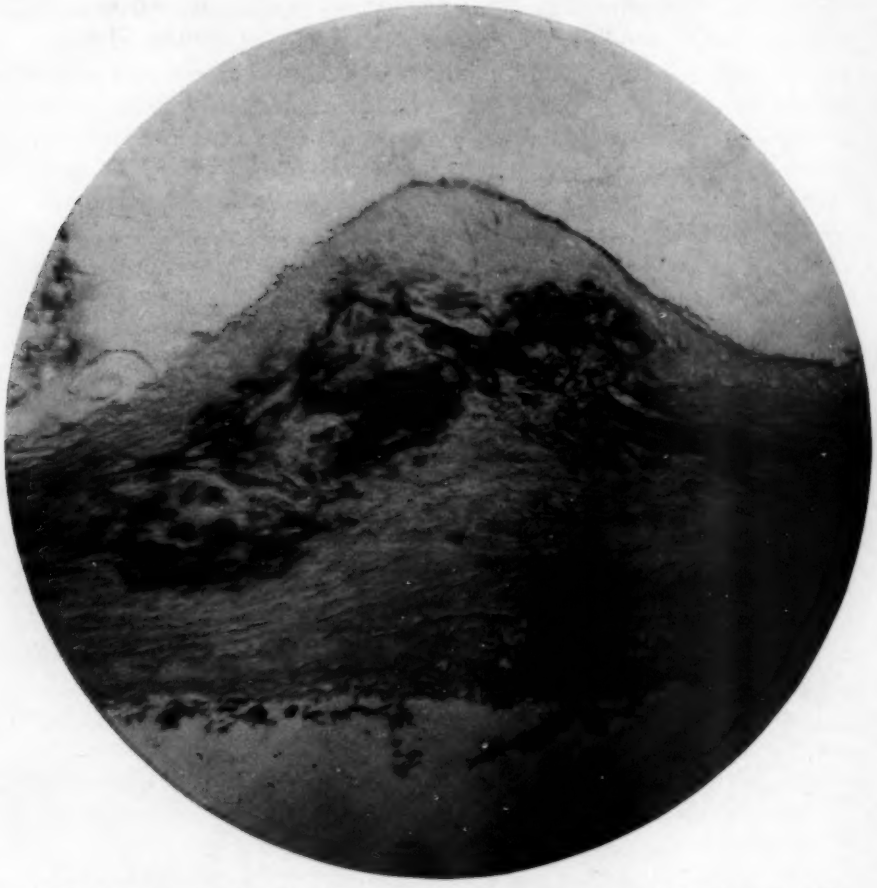

Fig. 4.—Arteriosclerosis of both types, showing extensive calcification of media and lipoid infiltration of intima.

these received only the barley and alfalfa diet, so that the pathologic changes encountered cannot be attributed to overfeeding of protein. In the second subgroup, which was fed the liver diet during the last year of the experiment in an attempt to make more pronounced the spontaneous changes already present, new processes may have been initiated, as it has been amply demonstrated that diets with high content of protein

are capable of causing vascular and renal injury in the rabbit (Newburgh and Clarkson,[2] Ignatowski,[5] Steinbliss,[6] et al.).

In the aortas of 4 of the animals of the first subgroup there was sclerosis of the raised intimal type. Medial sclerosis was also present in 1 of these. The process in 3 of the animals was limited to the root and arch of the aorta, and consisted of discrete elevated plaques not over 2 mm. in diameter, scattered over the surface of the wall. The aorta of the fourth animal, in which both types of sclerosis were present, was diffusely involved down to the diaphragm, very little normal intima remaining, while there was an advanced degree of calcification of the media. In one instance, the aortic valve was involved by extension of the process from the vessel wall. Marked renal changes were present eight times in this group of 10 animals. The histologic picture will be described later.

The aortas of 8 of the animals in the second subgroup of 10 (liver diet) were changed similarly, but more extensively. The process was confined to the intima, and in 2 instances the wall of the vessel was involved throughout its entire length down to the iliac bifurcation, with a thrombosis of the abdominal portion in 1. In the other 6 instances, the wall of the root and arch of the aorta contained many diffusely scattered arteriosclerotic plaques. The kidneys were involved in 9 of the 10 animals comprising the group.

A further study was made of the coronary arteries and of the arterioles in various organs (heart, liver, spleen and lungs) of the 20 animals with spontaneous nephritis. No coronary sclerosis was encountered in the first subgroup. The pulmonary and splenic arterioles were thickened in one of the animals, the pulmonary arterioles alone in another. Coronary sclerosis was present in 3 of the 10 that had received the liver diet. It consisted of minute yellowish papules, just discernible to the naked eye, limited to the region of the ostium and proximal 2 cm. to the left coronary artery. The lumen of the vessel was not encroached on, and there was no calcification. The splenic arterioles were thickened twice, and those of the lungs four times, in the animals of this second subgroup. Histologically, the arteriolar thickening was characterized by medial hypertrophy and intimal hyperplasia.

Degeneration of the myocardium or disease of the arterioles and capillaries of the coronary circulation was not found in any of the 20 rabbits.

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5. Ignatowski: Ueber die Wirkung des tieren Eiwesses auf die Aorta und die parenchymatösen Organe des Kaninchens, Virchows Arch. f. path. Anat. **198**: 248, 1909.

6. Steinbliss, W.: Ueber experimentelle alimentäre Atherosklerose, Virchows Arch. f. path. Anat. **212**:152, 1913.

Pronounced alterations of the kidneys were encountered histologically in 17 of the group of 20 rabbits. They were diffuse, involving all the renal structures in every instance and varying only in degree. Newburgh and Clarkson [7] stated that the pathologic process in the spontaneous nephritis of rabbits is characteristically of focal type, being limited to small foci of scarring throughout the kidney with intervening regions

Fig. 5.—Spontaneous diffuse nephritis. The dilated tubules contain hyaline casts. Glomerular tufts are adherent to the capsules. A diffuse overgrowth of interstitial tissue is seen.

of normal parenchyma, whereas the nephritis produced experimentally by feeding a diet having a high content of protein consists primarily of degenerative changes in the tubular apparatus. It will be remembered

7. Newburgh, L. H., and Clarkson, S.: Renal Injury Produced in Rabbits by Diets Containing Meat, Arch. Int. Med. **32**:850, 1923.

that in the group of 190 normal rabbits first discussed, spontaneous nephritis was encountered on histologic examination in 4 instances. In 2 of these the disease was of a distinctly focal type, corresponding in every detail to the description by Newburgh and Clarkson. In the others, however, the process was diffuse and identical with that occurring in 17 of the 20 animals selected because of clinical evidence of nephritis,

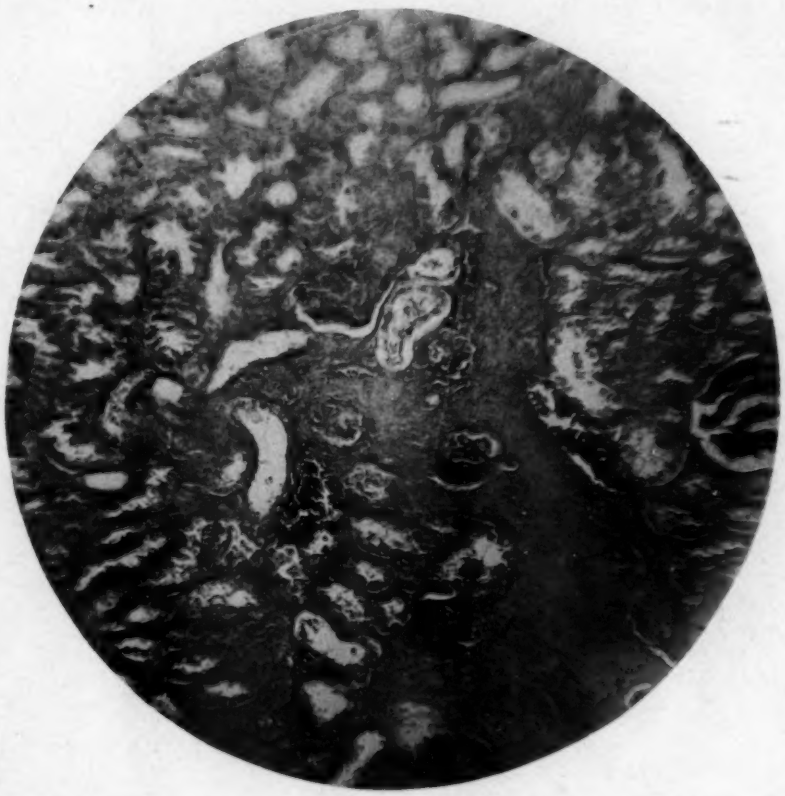

Fig. 6.—Spontaneous focal nephritis. Note area of scarring involving all the renal structures.

and similar in appearance to the renal changes produced by us in the experimental feeding of diets with high content of protein.[8]

Histologically, in this type of diffuse nephritis, there is a thickening of Bowman's capsule and often fusion between it and the glomerular tuft. Further changes are manifested by increased cellularity of the tuft, absence of red blood cells within the glomerular capillaries and, in

8. Nuzum, F. R.: Changes in the Kidney in Animals with Increased Blood Pressures While on High Protein Diets, Arch. Int. Med. **40**:364, 1927.

some instances, if the process is progressive, intracapillary thrombosis, hyalinization and, as an end-stage, partial to complete replacement of the glomerulus by fibrous tissue. The changes of the tubules consist of dilatation, flattening of the cells lining the tubules, with epithelial desquamation and necrosis in some instances, and the presence of many hyaline casts within the dilated lumina. These alterations are usually most evident in the loops of Henle and the collecting tubules, but in many instances no part of the tubular apparatus is spared.

A diffuse increase of interstitial tissue, with small areas of round cell infiltration about the diseased tubules, is sometimes apparent. More often there are focal areas of scarring throughout the cortex, involving all of the renal structures in the fibrous mesh. These scars are similar in appearance to the focal lesions of spontaneous nephritis previously mentioned. In each instance in which they were present in this group of animals, however, diffuse changes of an advanced degree were also found. It is probable that they are distinct from the diffuse process and represent a healed spontaneous nephritis of focal type resulting from an injury of an earlier date to the kidney. The fact that this focal scarring was always accompanied by advanced diffuse alterations suggests that it may have predisposed the kidney to further injury by decreasing the tissue reserve. Since the diffuse lesion often occurred in the absence of such previous scarring, it is evident that the latter scarring is not a necessary precursor of it. Likewise, as noted in the histologic examination of the kidneys of 190 normal rabbits, focal scarring may occur without accompanying diffuse changes.

The vessels are typically altered in most instances, especially those of the medullary rays. The walls appear almost uniformly thickened, apparently owing to hypertrophy of the media. The intima is thrown into folds, and the lumen of the vessel is decreased in size (figs. 7 and 8). Thrombosis or hyalinization of the renal vessels is not encountered.

These histologic changes were encountered in the kidneys of 17 of the 20 rabbits comprising the group with clinical spontaneous nephritis. In the kidneys of the remaining 3 animals, the changes were so slight that they could not properly be classified as diffuse nephritis. The walls of the vessels showed slight thickening. The glomerular capsules were definitely thickened, and in one instance the glomerular tufts were adherent. Occasionally, a dilated tubule was seen, but the tubular cells appeared unaltered, and no casts were found. Slight though these alterations were, it was felt that they represented a beginning stage of what would have developed later into a typical diffuse nephritis, had the experiment been continued for a longer period of time.

We have previously noted the similarity between the types of sclerosis occurring in the aortas of our animals and the common arteriosclerotic

processes affecting the larger arteries of man. A further comparison may be made between the arteriolar disease of the rabbit and that described as occurring in hypertensive diseases of man.

In the kidneys of the 20 animals with spontaneous nephritis, all of which had elevated blood pressures, medial hypertrophy of the inter-

Fig. 7.—Arteriolar thickening in spontaneous diffuse nephritis. Note also round cell infiltration about the diseased tubules.

lobular arterioles of the kidney was a constant observation. In the lungs and spleen of several of the animals, arteriolar thickening was found. There were both medial hypertrophy and intimal hyperplasia. Fishberg,[9] in a study of the anatomic observations in essential hyper-

9. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650, 1925.

tension, found arteriolar changes in the kidneys as a constant accompaniment of the disease. The splenic arterioles were affected in two-thirds of his 72 cases; the pancreatic in one-half; the hepatic in less than one-third; the cerebral in less than one-fifth. Histologically, the afferent renal vessels first showed a deposition of hyaline material beneath the endothelium, with later fatty changes. In the interlobular arteries, a

Fig. 8.—Cross-section of a thickened renal vessel. The media is hypertrophied; the intima thrown into folds.

hyperplasia of the internal elastic lamina was followed by infiltrative phenomena, connective tissue proliferation, medial atrophy and replacement by connective tissue. He did not find hypertrophy of the media in this series, but in a later communication [10] stated that he had seen it in the arcuate renal arteries in instances of long-standing glomerular

10. Fishberg, A. M.: The Arteriolar Lesions of Glomerular Nephritis, Arch. Int. Med. **40**:80, 1927.

nephritis. The primary change in the arterioles of other organs was hyalinization.

Medial hypertrophy of the arterioles, the most frequently occurring lesion in the kidneys of our animals, has been noted as a pathologic feature of hypertension in man by many observers. Allbutt [11] said that "in cases of high arterial pressures, whether it be a true muscular hypertrophy or not, at any rate a thickening of the media is obvious. . . ." Volhard and Baehr (quoted by Fishberg) noted both its presence and its absence in essential hypertension. Keith, Wagener and Kernohan,[12] in a postmortem study of 7 instances of malignant hypertension (hypertension combined with severe neuroretinitis and normal renal function) found intimal hyperplasia and medial hypertrophy in the arterioles of all organs and tissues of the body. We recently studied the microscopic sections from an instance of malignant hypertension, and were struck by the similarity in appearance that the arteriolar lesions occurring in experimental animals bear to the generalized arteriolar-capillary disease characteristic of this condition.

While we do not wish to say positively that the arteriolar lesions accompanying long-standing hypertension in man are identical with those occurring in the rabbit, yet it is certain that they are morphologically similar, and it seems possible that the mechanism of production may be the same in both. Our rabbits had elevated blood pressures over a period of almost three years, comparable to a duration of half a lifetime in man. The response of the vascular tissues to this prolonged strain theoretically might be of the same character as that occurring in man under similar circumstances. Although the pathologic process in man and animal may show differences in distribution and minor histologic detail, it is probable that the changes observed in both instances represent a reparative-degenerative response of the vessel wall to increased intravascular tension.

COMMENT

The two types of spontaneous sclerosis described by us are not strictly in accord with the results of other observers, who have often failed to distinguish clearly between these two processes, or have simply described calcification of the media as the distinctive pathologic change. It is important to recognize the fact that sclerosis of the intimal or raised type can occur spontaneously, because it is the one that results from the experimental feeding of diets having a high content of protein

11. Allbutt, T. C.: Arteriosclerosis, New York, The Macmillan Company, 1925, p. 32.

12. Keith, M. N.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141, 1928.

(or cholesterol). That its spontaneous occurrence is comparatively rare, however, is indicated by the fact that it was encountered only six times, or in 3.1 per cent, of our series of 190 rabbits, while medial calcification, or the depressed type, was present spontaneously in 11 instances, or in 5.8 per cent of the group. These types of arteriosclerosis, when occurring spontaneously, are for the most part limited to small areas, but in exceptional instances may cover the greater part of the aortic wall. This was true of 2 animals, or 1 per cent of the entire group of 190 rabbits.

The sclerosis of the aorta that was found in 18 of the 20 rabbits with spontaneous nephritis is identical histologically with these two types. The feeding of a liver diet to 10 of these animals served to exaggerate the process. If, on the other hand, the sclerosis in this group of 10 is to be regarded as having been experimentally produced (a justifiable inference, because it occurred in 8 instances, or in 80 per cent of the group, and because it was marked in degree and extent), it is seen to be identical with that occurring spontaneously. The question as to whether or not the thickening of the splenic and pulmonary arterioles is a spontaneous process cannot be answered at this time.

We believe also that spontaneous nephritis may occur in two types. The first is focal, as described by Newburgh and Clarkson, and is of comparatively rare occurrence, as it was encountered only twice, or in 1 per cent of 190 normal rabbits used in this study. It probably does not produce clinical evidence of nephritis. The second type is diffuse, little of the renal tissue escaping injury. Casts and albumin appear in the urine; there are retention of nitrogen bodies in the blood and elevation of blood pressure. It is similar histologically to the nephritis produced by feeding experiments, and is comparable to chronic diffuse nephritis in man.

We are uncertain as to the etiologic factors involved in these spontaneous changes. It will be remembered that our normal animals were fed a stock diet of barley, 52 Gm., and alfalfa, 150 Gm., daily throughout life. On analysis, this diet is shown to contain 14.2 per cent of protein. Much evidence has been accumulated that diets with high content of protein are capable of injuring the kidneys and blood vessels of rabbits, but this percentage of protein is less than any used successfully, to our knowledge, to produce such changes. In a previous experiment,[13] we produced arteriosclerosis of the raised intimal type in 7 of 11 animals fed an oat diet containing 16 per cent protein, over a period of two years.

13. Nuzum, F. R.; Seegal, B.; Garland, R., and Osborne, M.: Arteriosclerosis and Increased Blood Pressure: Experimental Production, Arch. Int. Med. **37**:733, 1926.

Nine of these animals had renal changes.[8] It may be that the high percentage of intimal sclerosis and of nephritis occurring in this group is attributable, at least in part, to the 14.2 per cent protein in the diet.

TABLE 1.—*Relation of Infection to Changes in the Aorta and Kidneys of Twenty Rabbits with Spontaneous Nephritis*

Rabbit and Diet	Infection: Nature	Infection: Duration, Mo.	Infection: Year	Arteriosclerosis of Aorta	Nephritis
Alfalfa and barley					
71	Abscess of feet..... Infection of ear.....	10 10	Second First	None	Very marked diffuse
66	Infection of ear..... Abscess of feet.....	4 15	First First and second	Arch, small plaques	Moderate diffuse
69	Abscess of breast.....	15	Second and third	Root and arch, confluent plaques	Very slight*
78	Infection of ear..... Abscess of foot.....	5 1	First Third	None	Slight diffuse
75	Infection of ear.....	5	First	Root to diaphragm (both types)	Slight diffuse
76	Infection of ear.....	3	First	Arch, two small plaques	Moderate diffuse
68	Abscess of feet.....	2	Third	None	Marked diffuse
61	Infection of ear..... Abscess of foot.....	1 1	First First	None	Moderate diffuse
73	Infection of ear.....	1	Second	None	Very slight*
62	None.....	..	.....	None	Very marked diffuse
Liver					
60	Infection of ear, pneumonia (terminal)	16	Second and third	Entire arch, confluent plaques	Moderate diffuse
63	Infection of ear..... Abscess of feet.....	2 6	Second First	Entire aorta, thrombosis abdominal portion	Very marked diffuse
67	Infection of ear.....	4	First	Arch, scattered plaques	Slight diffuse
70	Infection of ear..... Abscess of leg, pneumonia (terminal)	4 1	First First	Arch, scattered plaques; aortic valve sclerotic	Moderate diffuse
65	Infection of ear..... Abscess of foot.....	2 1	Second Second	None	Moderate diffuse
64	Infection of ear, pneumonia (terminal)	3	First	None	Moderate diffuse
79	Infection of ear.....	3	First	Entire aorta, confluent plaques	Moderate diffuse
77	Infection of ear..... Abscess of foot.....	1 2	First Second	Arch, scattered plaques	Very slight*
72	Infection of ear, pneumonia (terminal)	2	First	Arch, scattered plaques	Slight diffuse
74	Abscess of leg, pneumonia (terminal)	1	First	Arch, scattered plaques	Slight diffuse

* Alterations limited to the vessels and glomerular capsules.

The possible rôle of infection in the production of these spontaneous changes should be considered. Several observers (Gilbert and Lyons,[14] Klotz[3] et al) have produced arterial lesions in rabbits by the intravenous injection of bacteria. Newburgh and Clarkson found renal

14. Gilbert and Lyons, quoted by Klotz (footnote 3).

changes of a focal type "fairly common" in 19 rabbits used as controls for their feeding experiments. These animals were purposely exposed to the infections prevalent in their laboratory animals. The vascular system in this group, however, was unaltered.

Table 1 shows the infections present in our group of 20 rabbits with spontaneous nephritis during the three year period of the experiment. The nature and duration of the infection, the year of its occurrence and the pathologic data in brief are presented for each animal. In the second column, the infections are arranged in sequence of decreasing severity and duration from above downward; this order being followed for the group of 10 animals that were fed the alfalfa and barley diet and for the group of 10 that were fed the liver diet. The infection of the ear listed so frequently consisted of a nonsuppurative parasitic disease of the external auditory canal. This disease, almost uniformly present in the early months of the experiment, was later eradicated by appropriate treatment. Abscess of the foot was a frequent complication. Pneumonia was a frequent terminal infection.

All the animals suffered from one or more of these infections at some time during the course of the experiment, with the exception of rabbit 62. This animal had, however, marked diffuse nephritis.

We were unable to determine any correlation between the character and duration of the infection and the degree and nature of the spontaneous changes in the kidneys and blood vessels.

SUMMARY

Spontaneous sclerosis of the arteries of rabbits occurs in two types, (1) an elevated intimal lesion and (2) a depression of the intima associated with medial calcification. These are pathologically unlike each other, but are identical with lesions produced experimentally. The incidence of the former type we found to be 3.1 per cent and of the latter, 5.3 per cent, in a group of 190 normal animals. Spontaneous nephritis, both focal and diffuse, occurred two times each, or in 2.1 per cent of this series. In this same group, spontaneous nephritis and arteriosclerosis did not occur together in a single instance.

In a second group of 20 animals, selected because of clinical evidence of spontaneous nephritis, the kidneys of 17 showed a diffuse nephritis similar histologically to that encountered twice in the first group, and to that produced experimentally by feeding diets with high content of protein. The kidneys of the remaining 3 animals presented slight vascular and glomerular changes.

Of these 20 animals, 10 were fed a liver diet for one year, and in the aortas of 8 of these 10, elevated intimal lesions were present. There

was no sclerosis of the depressed type. Diffuse renal lesions were present in 9. Of the remaining 10 animals, 4 presented elevated sclerosis, 1 both types, and 8 diffuse nephritis.

A study of the coronary arteries and arterioles of the heart, liver, spleen and lungs in this group of 20 animals was made. In the 10 not fed liver, there was no coronary sclerosis. The pulmonary and splenic arterioles were thickened in 1 animal; the pulmonary arterioles alone in another. In the 10 fed liver, coronary sclerosis of slight degree was present three times, thickening of the splenic arterioles twice and thickening of the pulmonary arterioles four times. Histologically, medial hypertrophy and intimal hyperplasia were present.

Disease of the coronary arterioles or myocardium was not found in these 20 animals.

The possible etiologic factors involved in these spontaneous changes are discussed.

CONCLUSIONS

The arteries of rabbits are subject to two types of spontaneous disease: (1) elevated intimal lesions and (2) intimal depressions overlying medial calcification. These changes occur infrequently in large groups of normal animals. They are histologically different from each other, but identical with lesions regarded as of experimental production, and similar to the common types of arteriosclerosis in man.

The kidneys of rabbits present also two types of spontaneous alteration: (1) focal nephritis and (2) diffuse nephritis. The renal alterations occur more infrequently than do the arterial lesions. These two types of spontaneous nephritis may occur separately or in combination and bear no relation to spontaneous vascular disease.

The focal type of spontaneous nephritis gives no clinical evidence of its presence. Histologically, it consists of small areas of scarring, involving a minimum of renal tissue, but all the renal structures in the diseased area. It may possibly predispose to the development of diffuse nephritis by reducing tissue reserve.

The diffuse type is manifested clinically by the presence of persistent albuminuria, cylindruria, alterations of the blood chemistry, decrease in phthalein excretion and increase in blood pressure. Histologically, it is identical with the nephritis thought to be produced by feeding of a diet having a high content of protein, and somewhat similar to chronic diffuse nephritis in man.

A liver diet with high content of protein fed to an animal with spontaneous nephritis of the diffuse type probably increases the renal injury, as judged clinically and pathologically. It also increases the

vascular disease already present spontaneously and initiates new vascular injury.

Disease of the arterioles of the lungs and spleen involving the media and intima, and disease of the coronary arteries, may occur in combination with diffuse nephritis. The arteriolar disease is morphologically similar to that described as occurring in the hypertensive diseases of man, and probably represents a response of the vascular wall to increased intravascular tension.

Infection plays little or no apparent causal rôle in the production of spontaneous vascular and renal disease in the rabbit.

SCLEROSIS OF THE PULMONARY ARTERY AND ARTERIOLES

A CLINICAL PATHOLOGIC ENTITY *

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Sclerosis of the pulmonary artery was first mentioned by Vieussens in 1706. It was over a hundred years before it was again described by Bouillaud and then in 1829, by Andral,[1] who noted pulmonary sclerosis in association with mitral stenosis. Laennec suspected these lesions in his description of infarcts of the lung, which he thought were of local origin and secondary to local formation of thrombi. However, Virchow's theory of their embolic origin was prevalent at that time (1856). It was not until more recently that the local formation of thrombi was proved (Rist and Roland,[2] Letulle and Jacquellin [3]).

Romberg [4] and Aust [5] described primary sclerosis of the pulmonary artery, but gave no explanation. Marchand [6] believed that increased intrapulmonary pressure resulted in pulmonary atherosclerosis. Ayerza [7] suggested syphilis as a factor and described a clinical syndrome of what he termed "black cardiacs" that accompanied this condition. Posselt [8] reviewed the conception of Andral and also mentioned primary atherosclerosis of the pulmonary artery.

The majority of the aforementioned observations were made macroscopically, and only the larger branches of the pulmonary artery

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1. Andral, G.: Malades des pulmones, Traite d'anatomie pathologique, 1829, vol. 2, p. 294.

2. Rist and Roland: Contribution a l'étude clinique, anatomique et pathogenique des infarcties et des hemorragies pulmonaires au cours de l'endocardite a evolution prolongée, Ann. de méd. **3**:20, 1926.

3. Letulle and Jacquellin: Aneurysme syphilitique de l'artere pulmonaire, Arch. d. mal. du coeur **13**:385, 1920.

4. Romberg, E.: Ueber Sklerose der Lungenarterie, Deutsches Arch. f. klin. Med. **48**:197, 1891.

5. Aust, C.: Casuisticher Beitrag zur Sklerose der Lungenarterie, München. med. Wchnschr. **39**:689, 1892.

6. Marchand: Ueber Arteriosklerose (Athero-Sklerose), Verhandl. d. Kong. f. inn. Med., 1904, p. 23.

7. Ayerza, L.: Ayerza's Disease, Rev. Soc. de méd. int. **6**:73, 1925.

8. Posselt, A.: Die Erkrankungen der Lungenschlagadern, Ergebn. d. allg. Path. u. path. Anat. **13**:298, 1909; Zur Pathologie und Klinik der primären Atherosklerosis pulmonalis, Wien. Arch. f. inn. Med. **11**:357, 1925.

were considered. In 1920, Eppinger and Wagner [9] described five cases of what they believed to be primary atherosclerosis of the smaller and larger branches of the pulmonary artery associated with the clinical syndrome as described by Ayerza, namely, cough, dyspnea, cyanosis, edema and marked hypertrophy of the right ventricle of the heart.

Lang [10] then showed that a thrombo-arteriolitis may be the origin of this clinical syndrome, and he believed that some of Eppinger's cases were infective.

Von Glahn and Pappenheimer [11] described rheumatic changes of the smaller pulmonary circulation (McClenahan and Paul [12]).

Primary arteriosclerosis and arteriolosclerosis of the pulmonary artery is rare. Thomas [13] in reviewing the literature found only 10 cases among 500 reported. (Monckeberg,[14] Rossle,[15] Tchistovich,[16] Vaquez,[17] Lowenstein,[18] Durand,[19] Eppinger and Wagner [9] and more recently Bacon and Apfelbach,[20] Warthin,[21] Clark, Coombs, Hadfield and Todd [22] and Steinberg [23] described changes in the intima only.)

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9. Eppinger, H., and Wagner, R.: Zur Pathologie der Lunge, Wien. Arch. f. inn. Med. **1**:83, 1920.

10. Lang, G.: Zur Frage der thrombo-arteriolitis pulmonaires, Deutsches Arch. f. klin. Med. **114**:539, 1924.

11. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **11**:235, 1926.

12. McClenahan, W. U., and Paul, J. R.: A Review of the Pleural and Pulmonary Lesions in Twenty-Eight Fatal Cases of Active Rheumatic Fever, Arch. Path. **8**:595, 1929.

13. Thomas, Marcel: Des affections acquises de l'artère pulmonaire, Thèse de Paris, no. 474, 1929.

14. Monckeberg: Ueber die genuine Arteriosklerose der Lungenarterie, Deutsche med. Wchnschr. **33**:143, 1907.

15. Rossle: Ueber Hypertrophie und Organkorrelation, München. med. Wchnschr. **8**:377, 1908.

16. Tchistovich: Thrombo-artérite obliterante pulmonaire chronique, Compt. rend. Soc. de biol. **2**:627, 1923.

17. Vaquez, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **26**:183, 1908.

18. Lowenstein, K.: Ueber Thromboarteriitis pulmonalis, Frankfurt. Ztschr. f. Path. **27**:226, 1922.

19. Durand, P.: L'endo-artérite primitive de l'artère pulmonaire, Thèse de Paris, 1927.

20. Bacon, C. M., and Apfelbach, C. W.: Primary Sclerosis of the Pulmonary Artery and Its Branches, Tr. Chicago Path. Soc. **12**:293, 1927.

21. Warthin, A. S.: A Case of Ayerza's Disease, Tr. A. Am. Phys. **34**:219, 1919.

22. Clark, R. C.; Coombs, C.; Hadfield, G., and Todd, A. T.: On Certain Abnormalities, Congenital and Acquired, of the Pulmonary Artery, Quart. J. Med. **21**:51, 1927.

23. Steinberg, Ulrich: Systematische Untersuchungen über die Arteriosklerose der Lungenschlagadern, Beitr. z. path. Anat. u. z. allg. Path. **82**:443, 1929.

Because of the lack of the right material it has been difficult to trace the pathologic development of this condition, and indeed some authors have questioned primary atherosclerosis of the pulmonary artery as an entity (Ayerza,[7] Arrillaga,[24] Escudero,[25] Warthin,[21] Hare and Ross [26]). These authors believed that syphilis plays the most important rôle.

The author has had the opportunity to study three cases of primary atherosclerosis of the pulmonary artery showing varying stages of the disease, so that its development could be studied. These observations justify primary arteriosclerosis and arteriolosclerosis of the lungs as a definite clinical and pathologic entity.

The three cases are presented in the order of their pathologic development.

CASE 1

History.—A white man, a Canadian, aged 45, complained on entrance into the hospital of dyspnea and cyanosis of one week's duration. He had been a tool-grinder, on and off, for fifteen years. Some years (?) before, he began to have a cough that was productive of a moderate amount of mucus varying in color from white to black. This did not trouble him markedly, and he did not heed it. About one year before, he noticed that his finger-tips and face were becoming blue, and three months before, he noted dyspnea on exertion. He continued to work, however, until one week before admittance, when he became markedly weak and cyanotic. No edema had been noted, but there had been some swelling of the abdomen for one month.

His past history and family history were essentially negative.

Physical Examination.—On examination, the patient was found to be obese, dyspneic and cyanotic, and from time to time he coughed. The temperature taken rectally was 99.6 F.; the pulse rate, 100; the respiration rate, 28, and the blood pressure 150 systolic and 90 diastolic.

The essential observations were as follows: The face, neck and extremities showed marked cyanosis. There was slightly increased resonance over the entire chest, with diminished tactile and vocal fremitus. The breath sounds were diminished slightly, but no abnormal sounds were heard. Because of the obesity, the borders of the heart were difficult to percuss. The tones were of fair quality and intensity and of regular rhythm and rate. The second pulmonic beat was accentuated. The abdomen was distended and tympanitic, with slight dulness in both flanks, but with no shifting dulness. There was no edema.

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24. Arrillaga, F. C.: Esclerosis secundaria de la arteria pulmonar y su cuadro clinico (Cardiacas Negros), These de Buenos Aires, 1912; Sclerose de l'artère pulmonaire secondaire à certains états pulmonaires chroniques, Arch. d. mal. du coeur **6**:518, 1913; Sclerose de l'artère pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:292, 1924.

25. Escudero, P.: Polycythemia and Erythreosis with Sclerosis of the Pulmonary Artery, Rev. Soc. de méd. int. **1**:463, 1925.

26. Hare, C. D., and Ross, J. M.: Syphilitic Disease of the Pulmonary Arteries, Lancet **2**:806, 1929.

Laboratory Examination.—The urine contained a trace of albumin. The Kahn reaction of the blood was negative. The carbon dioxide combining power was 46. The urea nitrogen was 23 mg., and the creatinine, 1.95 mg., per hundred cubic centimeters of blood. No blood count was recorded.

Course.—The patient remained in the hospital for six days, during which his cyanosis deepened. He became irrational, sank into a stupor and died.

Clinical Diagnosis.—The clinical diagnosis was: Pulmonary arteriosclerosis with enlargement of the right side of the heart or pneumonoconiosis.

Postmortem Examination (Dr. R. H. Jaffé).—The body weighed 171 pounds (77.6 Kg.) and was 159 cm. in length.

Externally there was marked cyanosis of the face and the chest, and over the neck deep purple patches varying in size from that of a pinpoint to that of a pinhead. The lower extremities were slightly edematous.

When the chest was opened, the lungs were found collapsed; the pleural cavities contained no fluid or adhesions. The lungs were subcrepitant to crepitant throughout. The surfaces made by sectioning were deep gray and smooth.

The heart weighed 460 Gm. The left ventricular wall was 18 mm. and the right ventricular wall was 5 mm. thick. The apex was formed by the right ventricle. The myocardium was reddish brown and moderately firm.

The aorta measured 60 mm. in circumference 1 cm. above the cusps. The intima was studded by a moderate number of hyaline and fatty plaques.

The pulmonary artery measured 90 mm. in circumference 1 cm. above the cusps. The intima of the main trunk and two main branches was smooth. In the branches of the first order there were slightly elevated, light yellow plaques, which became more numerous and confluent in the branches of the third and fourth order.

The kidneys, spleen and liver were deeply cyanotic and moist with blood.

The bone-marrow was deep red.

Microscopic Examination.—In the larger bronchi, the mucosa was slightly thickened by an increase in fibrous tissue and dilated capillaries. The epithelium in focal areas was composed of two or three layers of transitional cells. The smaller bronchi were filled with desquamated and degenerated epithelial cells and erythrocytes. There was no round cell infiltration or peribronchial fibrosis.

The alveoli of the lungs were moderately to markedly distended. Their walls in some instances were thicker than normal because of capillary dilatation and accumulations of large cells that contained black and brown pigment. In other places, the alveolar walls were thin and composed of fibrous and hyaline tissue in which were scattered pyknotic nuclei. These walls were poor in elastic fibers.

In the intrapulmonary arteries up to 0.2 mm. in diameter, the intima in most instances, showed no change. In a few of these vessels, the intima was slightly thickened. The subendothelial layer contained a hyaline substance that stained red by Van Gieson's method. The inner elastic membrane in a few vessels was split. The media showed the most constant change. There was a definite increase in its thickness, which was due in greatest part to an increase in elastic fibers and to a less extent to hypertrophy of the muscle fibers. Occasionally, adjoining the internal elastic membrane were large spaces, each containing a pyknotic nucleus. The adventitia was unchanged. There was no round cell infiltration. An occasional fibrin thrombus was seen in the lumen.

Intrapulmonary vessels from 0.2 to 0.4 mm. in diameter, in the majority of instances, were unchanged. Occasionally there was a slight thickening of the intima, especially of the subintimal layer, and also a thickening of the internal

elastic membrane. The media was slightly thickened, owing to an increase of elastic tissue. The adventitia was unchanged. There were no thrombi in these vessels.

Intrapulmonary vessels over 0.4 mm. in diameter were practically unchanged, except for a slight thickening of the internal elastic membrane.

No organisms were found in the walls of the larger or smaller intrapulmonary vessels of the lung by the Gram-Weigert method.

In the extrapulmonary arteries, there was an increase in the size of the media due to an increase of elastic tissue and a hypertrophy of the muscle fibers. The intima was slightly thickened subendothelially by large pseudoxanthomatous cells The adventitia was unchanged.

The intima of the aorta was thickened by large hyaline plaques with central deposits of lipoid material. Pseudoxanthomatous cells were scattered focally in the subendothelial layer. The media in these areas was reduced in size, whereas in the intervening areas it was of normal thickness. The adventitia was unchanged.

The veins were collapsed and filled with a small amount of blood. No changes in their walls were noted.

In the wall of the left ventricle of the heart, the muscle fibers were slightly thicker than normal, and their cross-striations were indistinct. There was a marked capillary hyperemia. The arterioles were dilated, but their walls were not thickened. In the wall of the right ventricle, the muscle fibers were markedly thickened; the nuclei were of irregular shape and rich in chromatin. The van Gieson stain showed no evidence of hyaline degeneration or scar formation.

The kidneys presented a moderate diffuse capillary hyperemia. Bowman's capsules were slightly thickened. The arterioles were practically unchanged. The medium and larger sized arteries showed no thickening of their walls. Sudan III preparations revealed no changes.

Throughout the liver and spleen there was marked capillary dilatation. The arteries and arterioles were unchanged.

Bone-marrow of the femur showed hyperemia and numerous foci of erythropoiesis and granulopoiesis.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: Arteriosclerosis of the pulmonary artery; eccentric hypertrophy of the heart, especially of the right ventricle; moderate sclerosis of the aorta and the coronary arteries; passive congestion of the lung, liver, spleen, kidneys and bone-marrow; recent hemorrhages in the gastric and intestinal mucosa and in the pancreas, and slight ascites.

CASE 2

History.—A white man, an Austrian, aged 48, who was a laborer in a cleaning and dyeing plant, on entering the hospital complained of dyspnea, cyanosis and anasarca of the dependent parts of the body. The patient had had a cough for many years, with expectoration of whitish mucus. About two years before, he became dyspneic and began to show edema of the lower extremities. He was treated at home and his heart soon became compensated. In the past two years he had had three similar attacks. In the last attack, his distress was more marked, with abdominal distention and marked cyanosis. The patient had been cyanotic for some time previously, but he did not know the exact length of time. Hematemesis or hemoptysis (the patient did not know which) was present with the last attack.

The past history and the family history were essentially negative.

Physical Examination.—Examination revealed a cyanotic, markedly dyspneic, well nourished man who was acutely ill. The temperature was 102.4 F.; the pulse rate, 144; the respiration rate, 36, and the blood pressure, 120 systolic and 100 diastolic. The chest in cross-section was oval; the expansion was equal on both sides, with normal vocal and tactile fremitus and normal resonance. Moist, sonorous inspiratory râles were heard over the entire chest. The heart was enlarged transversely. The apex was 12.5 cm. to the left of the midsternal line, and the right border was 2.5 cm. to the right of the right sternal margin. The heart tones were regular in rate and rhythm. No murmurs were audible. The abdomen was distended with fluid. There was a pitting edema that extended up to and included the abdominal wall.

As the patient died shortly after he entered the hospital, no laboratory studies were possible.

Clinical Diagnosis.—The clinical diagnosis was: Cardiorenal disease with decompensation.

Postmortem Examination (Dr. R. H. Jaffé).—The body weighed 175 pounds (79.4 Kg.) and was 148 cm. in length.

Externally there was severe cyanosis of the face, neck and extremities, with recent hemorrhages about the nares. There was marked edema of the lower extremities, scrotum and abdominal wall.

When the chest was opened, the lungs were found moderately distended. The pleural cavities were normal, except for few fibrinous adhesions on the left side. The lungs were subcrepitant to crepitant, and presented numerous small palpable nodules throughout. The surfaces made by section were gray, except in the left lower lobe, where there were several discrete, red, granular areas of consolidation.

The heart weighed 520 Gm. The left ventricular wall was 14 mm. and the right ventricular wall was 7 mm. thick. The myocardium was firm and reddish brown. The right ventricle was dilated. The endocardium of the left ventricle was thickened and grayish white.

The circumference of the aorta was 70 mm. 1 cm. above the cusps. The intima was smooth.

The intima of the coronary arteries contained a few hyaline plaques.

The circumference of the pulmonary artery was 90 mm. Numerous yellow plaques as much as 4 mm. in diameter were found throughout the vessel, but were most marked in branches of the second and third order.

The kidneys, spleen and liver were deep purple and moist with blood.

Bone-marrow from the femur was deep red.

Microscopic Examination.—The mucosa of the larger bronchi in places was lined by transitional cells. In these areas, the cells were piled up in several layers and showed many mitotic figures. The walls were thickened, hyperemic and loosely infiltrated by lymphocytes. In the cartilage, the capsules of the cells were calcified. The smaller bronchi were filled with degenerated desquamated epithelial cells. There were many small, anthracotic fibrotic foci at the angles of the septums.

In places, the alveolar walls were moderately thickened by an increase in fibrous tissue and a capillary hyperemia. There were accumulations of round and spindle-shaped cells. The round cells had large oval nuclei and ample oxyphilic cytoplasm and in many instances contained a granular black pigment. In other places, the alveolar septums were narrow and composed only of fibrous strands that contained pyknotic nuclei (van Gieson's stain). There was a diminished amount of elastic tissue, and in places it was entirely absent. In these areas, the arterioles showed their greatest degenerative changes.

In intrapulmonary arteries up to 0.2 mm. in diameter, the intima, as a rule, was markedly thickened. There was a splitting of the internal elastic membrane, with an increase of elastic fibers. At times, this was associated with proliferation of fibroblasts, and at other times with hyaline and fatty changes of the subendothelial region. Thrombi were seen in varying stages of organization. The media was uniformly thickened. There was an increase in the elastic and fibrous tissue. In a large number of instances, large spaces, each containing a pyknotic nucleus, were evident, with hyaline changes, especially adjacent to the internal elastic membrane. The adventitia was unchanged.

In intrapulmonary vessels from 0.2 to 0.4 mm. in diameter, the intima in many instances was thickened owing to subendothelial proliferation of fibroblasts and hyaline degeneration. The condition of the internal elastic membrane varied from a moderate thickening to a splitting with an increase of elastic fibers. There were occasional nodular thickenings of the intima, which were covered by endothelium and contained spindle-shaped cells, fibrous tissue and fine elastic fibrils. In some places, small fibrin thrombi covered these nodules. The media was uniformly thickened. There was an increase in elastic and muscular tissue. Large spaces, each with a pyknotic nucleus, were evident sporadically. The adventitia was unchanged.

In intrapulmonary vessels over 0.4 mm. in diameter, changes were noted similar to those in the medium-sized arteries, but not as marked.

Gram-Weigert stains did not reveal the presence of organisms in the walls of intrapulmonary arteries or in their thrombi.

In extrapulmonary arteries, the intima was thickened subendothelially. There was a proliferation of spindle-shaped cells and fibrous tissue. Large pseudoxanthomatous cells were present throughout. The internal elastic membrane was thickened and in some instances showed splitting. The media was thickened by an increase in elastic fibers and a hypertrophy of the muscle fibers. The adventitia was unchanged.

In the aorta, the intima was only slightly thickened by pseudoxanthomatous cells and fibrous tissue. The internal elastic membrane was slightly thickened. The media and adventitia were unchanged.

The veins were collapsed. The intima was thickened in places and formed crescentic areas that were composed of hyaline connective tissue. The lumina were occasionally filled by fibrin thrombi. The internal and external elastic membranes sometimes approximated each other and gave a homogeneous purple color by means of the elastica stain.

The kidneys revealed a moderate diffuse capillary hyperemia. The arterioles were slightly thickened subintimally. The medium and larger sized arteries showed similar thickenings. Sudan III preparations showed accumulations of fat droplets in the basal portions of the epithelium of the convoluted tubules.

The liver and the spleen presented marked capillary dilatation throughout. There were no arterial changes.

In bone-marrow from the femur, the capillaries were diffusely dilated, and areas of erythropoiesis and granulopoiesis were numerous. The nuclei of the megakaryocytes were occasionally pyknotic.

Anatomic Diagnosis.—The anatomic diagnosis was: Arteriosclerosis of the pulmonary artery; eccentric hypertrophy of the heart, especially of the right ventricle; diffuse chronic bronchitis and focal bronchopneumonia; severe chronic passive congestion of the liver, kidneys, spleen, gastro-intestinal tract and bone-marrow, and edema of the lower extremities and genitalia.

CASE 3

History.—A white man, a Pole, aged 43, a stone-grinder, complained of dyspnea, cyanosis, edema of the lower extremities and weakness. He had had a cough for many years. Four years before admittance to the hospital, he became dyspneic and weak. He soon began to show edema of the lower extremities. Since that time he had had similar attacks.

About one year before, he entered the hospital in a semistuporous condition, with puffiness of the face and marked cyanosis of the face and extremities. The essential observation at this time was hyperresonance of the chest, with normal breath sounds, except in the bases, where a few moist râles were heard. The heart was essentially normal. The red cell count varied from 4,500,000 to 5,500,000. The white cell count was around 12,000, with a predominance of polymorphonuclear leukocytes. No abnormal cells were seen. The diagnosis at this time rested between polycythemia vera of Vacque's type and angioneurotic edema. The patient remained in the hospital for ten days. Under rest and treatment with atropine sulphate, he was soon up and about and comfortable. The cyanosis continued, but was of less extent. Thereafter the patient fared moderately well until one month before his last admittance; then all of his symptoms returned, and in addition his voice assumed the character of a croak. His cyanosis was out of proportion to his dyspnea, which was slight.

Physical Examination.—The temperature on entrance was 98.4 F.; the pulse rate, 104; the respiration rate, 28; the blood pressure, 120 systolic and 105 diastolic. The essential observations were marked dilatation of the vessels of the face and neck and deep cyanosis that included the entire body. The chest was barrel-shaped and was hyperresonant throughout, and there were moist râles in both bases. The breath sounds were slightly diminished. The heart was enlarged, especially the right ventricle. There was a systolic murmur over the apex. The abdomen was distended, with shifting dulness. The liver was three fingerbreadths below the right costal margin. There was marked edema of the lower extremities and the abdominal wall.

Laboratory Examination.—The patient remained in the hospital for two weeks. During this time, the red blood corpuscles varied from 6,690,000 to 6,280,000. The white cell count was 11,150. The x-ray picture showed marked enlargement of the heart, especially of the right ventricle. The Kahn reaction of the blood was negative. The urine contained albumin (four plus), but no casts.

Course.—Under treatment with digitalis, the patient improved for a time; then the cyanosis deepened, the respirations became more labored and on the day of his death, the temperature taken rectally rose to 101 F.

Clinical Diagnosis.—The clinical diagnosis remained the same as at the time of his previous stay in the hospital, with the addition of failure of the right side of the heart and chronic emphysema. Because of the croaking voice, mediastinal tumor, aneurysm of the aorta and mediastinal lymph glands pressing on the trachea and superior vena cava were each considered.

Postmortem Examination (Dr. R. H. Jaffé).—The body weighed 154 pounds (69.9 Kg.) and was 162 cm. in length.

The skin over the entire body was deep purplish gray. The eyelids were edematous; there were bilateral chemosis and marked conjunctival injection. The mucosa of the mouth was deep purple, and the oral cavity was filled with blood. The lower extremities, the scrotum and penis and the abdominal wall were all firmly edematous.

The abdominal cavity contained 1,500 cc. of a clear, straw-colored fluid. The liver was 8 cm. below the xyphoid process and 5 cm. below the right costal arch.

The pleural cavities contained, the right, 100 cc., and the left, 600 cc., of clear fluid. There were edematous fibrous adhesions about the lateral aspect of the right lobe.

The pericardial sac contained 250 cc. of clear fluid. The heart weighed 530 Gm. The apex was formed by the right ventricle. The wall of the left ventricle measured 19 mm.; the wall of the right ventricle in the region of the conus measured 12 mm., and near the apex 11 mm. The trabeculae and papillary muscles of the right ventricle were prominent. The epicardium showed numerous irregular, anastomosing, whitish plaques and pinpoint-sized deep red patches. The myocardium was reddish brown and firm.

The circumference of the aorta was 73 mm. There were few yellow plaques in the abdominal portion.

The circumference of the pulmonary artery was 90 mm. The intima of the larger branches was smooth. In the branches of third and fourth order, there were hyaline plaques arranged longitudinally.

The intima of the coronary arteries was smooth, except for a light yellow plaque in the descending portion.

The upper and middle lobes of the right lung were distended and crepitant. The lower lobe was compressed and subcrepitant. The cut surface was deep purplish gray, mottled with black and moderately moist. The lobes of the left lung were distended, and the edges were feathery. The cut surface was purplish gray and moderately moist.

The mucosa of the bronchi was purplish red and covered by a moderate amount of mucus.

The mucosa of the larynx was smooth and light purple.

The liver, kidneys and spleen were deep purple and moist with blood.

The bone-marrow of the femur was deep red.

Microscopic Examination.—The mucosa of the larger bronchi was slightly thickened by capillary dilatation and an increase of the fibrous tissue. The lumina were wide and filled with desquamated epithelium and red blood cells. The smaller bronchi were dilated; the epithelium was flattened and in places desquamated.

The alveoli of the lungs were wide and their septums thin. In many instances, the septums adjoining the alveoli were absent. In places, the alveolar walls were replaced by fibrous and hyaline tissue that contained pyknotic nuclei. The elastic content of these was markedly diminished or absent. In other areas, the septums were evidenced by dilated capillaries and large cells laden with black pigment. These cells in places arranged themselves about vessels and formed nodules that occasionally were transformed into fibrous tissue.

In intrapulmonary arteries up to 0.2 mm. in diameter, the intima, in most instances, was thickened and, in places, completely occluded the lumen. This thickening was the result of a subendothelial increase of fibrous tissue or hyaline degeneration of this tissue and accumulations of large pseudoxanthomatous cells. In some instances there was a nodular protrusion into the lumen which was covered by endothelium and was composed of young fibroblasts, connective tissue and hyaline material. Fine elastic fibrils were numerous. In the vessels in which the entire lumen was occluded there were small canals that were lined by endothelium and filled with blood. This type of intimal thickening was of a structure similar to that of the intimal nodules described. The internal elastic membrane was split, and there was an increase of the elastic tissue, most marked

on the intimal side. The media in most instances was reduced in size, owing to a decrease in elastic and muscle fibers and a replacement by hyaline and fibrous tissue. The adventitia was unchanged.

In intrapulmonary vessels from 0.2 to 0.4 mm. in diameter, the intima showed changes similar to those just described. The media, however, was thickened by an increased amount of fibrous and elastic tissue. In some instances, hyaline changes had taken place, but in the region of the nodules the media was much reduced in size. The adventitia was unchanged.

In intrapulmonary vessels over 0.4 mm. in diameter, the intima showed only a subendothelial thickening, but occasionally changes similar to those described were noted, with nodule formation, obliteration of the lumen and canalization. In several instances, hyaline thrombi had attached themselves to the nodular protrusions. The internal elastic membrane was thickened and occasionally split with an increase of elastic fibers. The media was also thickened as a result of this increase in elastic fibers, and in addition there was a hypertrophy of the muscle fibers. Large spaces, each filled with a pyknotic nucleus, were noted near the internal elastic membrane. The adventitia was unchanged.

No organisms were found by the Gram-Weigert method in the walls of intrapulmonary arteries or in the thrombi.

In extrapulmonary arteries, the intima was thickened in circumscribed areas, which were composed of dense connective tissue, poor in cells, with irregular interstitial spaces. Hyaline changes were also present. The internal elastic membrane was moderately thickened. The media was widened by an increase of elastic fibers and hypertrophy of the muscular elements. There was some evidence of fibrous tissue and hyaline changes. The adventitia was unchanged.

The walls of the veins appeared reduced in width, the elastic membranes in some instances approximating each other. There were subintimal circumscribed thickenings due to fibrous tissue and hyaline changes. In other instances there were organized thrombi with canalization.

In the right ventricle of the heart, the muscle fibers were distinctly thicker than normal. Their cross-striations were indistinct, sometimes to the point of absence. Several irregular areas within the muscle bundles stained deep red by van Gieson's method. The smaller arteries appeared unchanged. In the left ventricle, the muscle fibers were slightly thicker than normal. Their cross-striations were indistinct.

The kidneys showed small subcapsular areas of atrophy of the renal parenchyma. In the remaining part, the structure was well preserved. In the basal part of the epithelium of the convoluted tubules, fine lipoid droplets were found. The arterioles were not more prominent than would be expected at this age. There was a slight thickening of the intima of the larger arteries.

The liver and the spleen showed marked capillary dilatation throughout. No changes were noted in the arteries.

In the bone-marrow, the capillaries were much dilated and filled with blood. Areas of granulopoiesis and erythropoiesis were numerous.

Anatomic Diagnosis.—The anatomic diagnosis was: Arteriosclerosis of the pulmonary artery; eccentric hypertrophy of the heart, especially of the right ventricle; chronic emphysema of the lungs; marked passive hyperemia of the spleen, kidneys, stomach, intestines, liver and bone-marrow; generalized anasarca, and petechial hemorrhages of the epicardium, renal pelvis, stomach and large intestines.

SUMMARY

Close scrutiny of the clinical and pathologic observations in the three cases reported reveals a definite progression of events, each of which will be discussed.

Clinical Aspects: Cough.—In each case, cough was the first symptom. It was not severe, as the patients did not mention it of their own volition, but rather after specific questioning. This accounts for the uncertainty of time element. The cough was productive of whitish mucus, and only in case 2 was it associated with a questionable hemoptysis.

Cyanosis.—Cyanosis was usually the first definite objective observation. In the first case, it was noted first one year before entrance to the hospital; in the second case, it was thought to have been present before decompensation, i.e., two years before entrance. In the last case, the patient did not compain of cyanosis, but he was unintelligent and did not speak English. He had been in the hospital on four occasions in a year's time, his only symptoms being deep cyanosis of the face, neck and extremities and a semistupor. As he stated that his past attacks were of a similar nature, it is taken for granted that cyanosis was present for the same period of time, or four years.

In every case, then, cyanosis preceded the symptoms of decompensation. The time element is in direct proportion to the severity of the pathologic changes.

Dyspnea.—Dyspnea developed soon after cyanosis and though possibly mild at first soon became marked. However, it was not proportional to the depth of cyanosis.

Edema.—With failure of the right side of the heart, edema developed similar to that of a left cardiac decompensation. In the first case, it was mild; in the second case, moderate, and in the last case, severe. The size of the hearts, the dilatation of the ventricles and the thickness of their walls were in direct relation to the severity of the clinical observations.

Blood Picture.—Unfortunately, the blood pictures in the first two cases were not recorded. In the last case, the red blood cell count was 6,690,000, a true polycythemia or erythremia. This will be explained later. The white cell count was not significant.

Age, Sex, Occupation.—The age of incidence varied from 43 to 48 years. All three patients were well nourished to obese white men. The occupation is important in that in each case it was associated with aspiration of either particulate matter or gases. This factor aids in the formulation of the pathogenesis, which is discussed later.

Pathologic Aspects: Pulmonary Artery.—Grossly, in all three cases, the main trunk of the pulmonary artery was moderately dilated and presented little or no evidence of atheromatous changes. Beginning with the second order, however, and extending to the smaller branches, the atheromatous changes became more marked. These changes were present in all the cases, but most pronounced in the last one.

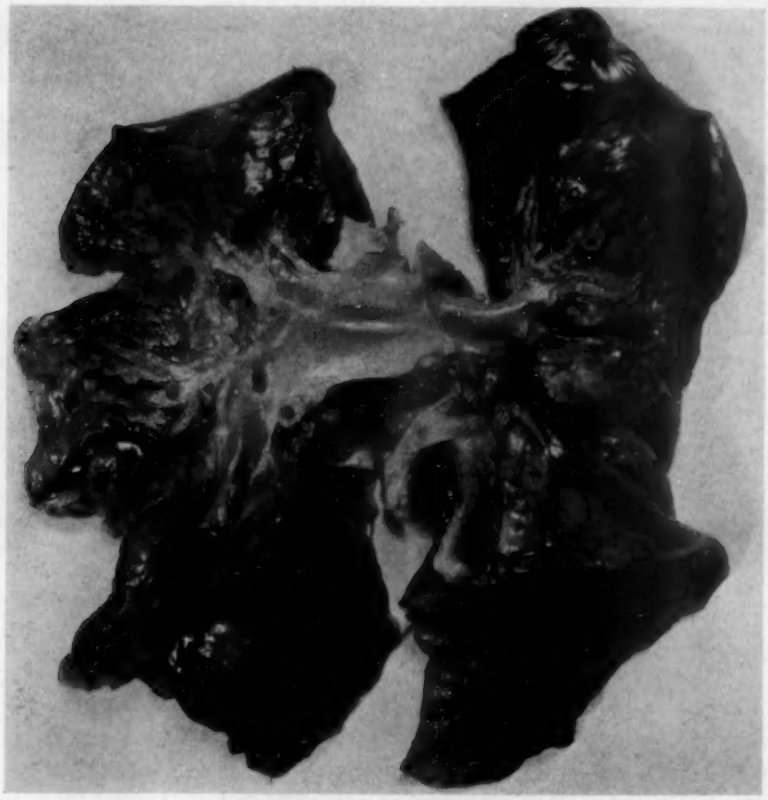

Fig. 1 (case 1).—The pulmonary artery is cut open to show the atherosclerotic plaques in the branches of the third and fourth order. The intima of the main trunk and its primary division is smooth.

Microscopically, the pathologic processes present in the three cases were similar, but in the first case only the small arteries were affected, in the second case, the small and medium sized ones, and in the last case all the intrapulmonary vessels.

The earliest changes were best noted in the small arteries in the first case. These changes consisted of a thickening of the media as the result of an increase of elastic tissue and a hypertrophy of the muscle fibers. The internal elastic membrane showed a longitudinal

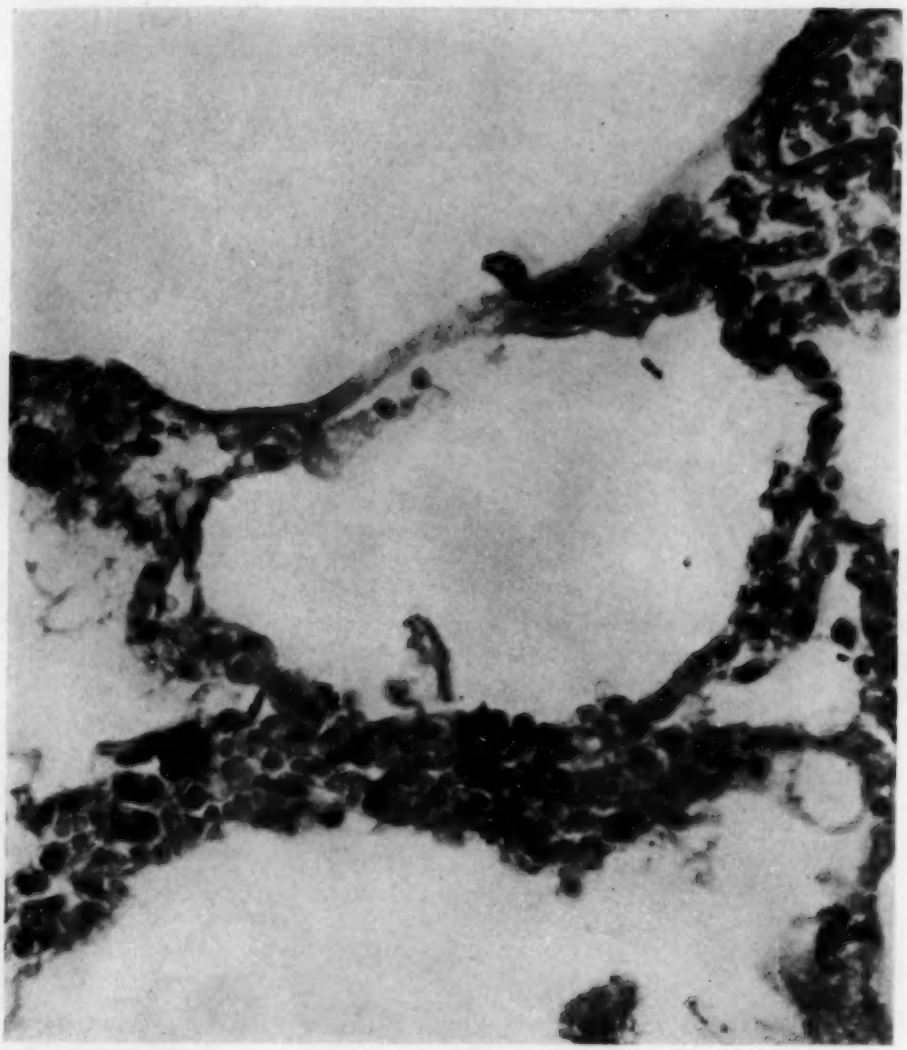

Fig. 2 (case 1).—An alveolus of the lung, showing capillary dilatation, capillary contraction and disappearance of the capillary endothelium with replacement of the alveolar wall by a homogeneous hyaline substance in which are found chromatin granules. (Hematoxylin and eosin; × 400.)

splitting with an increase of elastic fibrils that extended into the media and intima. In occasional vessels, the changes in the media were associated with a degenerative process that consisted of large clear spaces, each containing a pyknotic nucleus, hyaline changes and fatty changes. Similar degenerative changes were noted in the intima of some vessels. Thrombi were present, but uncommon.

In the second case, this process had progressed further. The intimal thickening was more generalized and showed further changes, with fibroblasts and fibrous tissue formation. The thrombi were present in larger numbers and showed various stages of organization, to canalization. The media in this case presented further regressive changes and was much reduced in thickness.

In the third case, there were arteries in which the lumina were obliterated, either by a proliferation of the intima or by organizing thrombi. Both of these processes were responsible for the occlusion of the lumina of the arteries, as in some instances this mass was rich in elastic fibrils, which would speak more for an intimal proliferation while in other instances only hyaline and fibrous tissue was present, which would speak for organized thrombi. It was impossible at times to come to a definite conclusion. The small nodular protrusions into the lumina of the arteries were a result of similar changes or of degenerative swellings of the media which caused the intima to protrude into the lumina. Young thrombi were at times attached to these nodules. The media in this case showed more marked degenerative changes and in some vessels was entirely replaced by fibrous tissue or was composed only of the internal and external elastic membranes, which approximated each other.

This progression of events affected the pulmonary artery and its branches in the order and with the severity mentioned.

Extrapulmonary Arteries.—The extrapulmonary vessels were the last to bear the burden of taxation and thus showed the least changes. There were slight thickening of the media and subintimal thickening due to pseudoxanthomatous cells and hyaline and fibrous changes.

Aorta.—Other than for a slight subintimal thickening with fatty changes, the aorta was unchanged.

Heart.—The heart in every instance was hypertrophic. The weights varied from 460 Gm. to 530 Gm. in direct relation to the severity of the pathologic changes. (The three patients were of about the same weight and height). The apexes, in the three instances, were made up by the right ventricles. The walls of the right ventricle were thickened, the thickening being only slight in the first case (5 mm.), moderate in the second case (7 mm.) and marked in the third case (12 mm.).

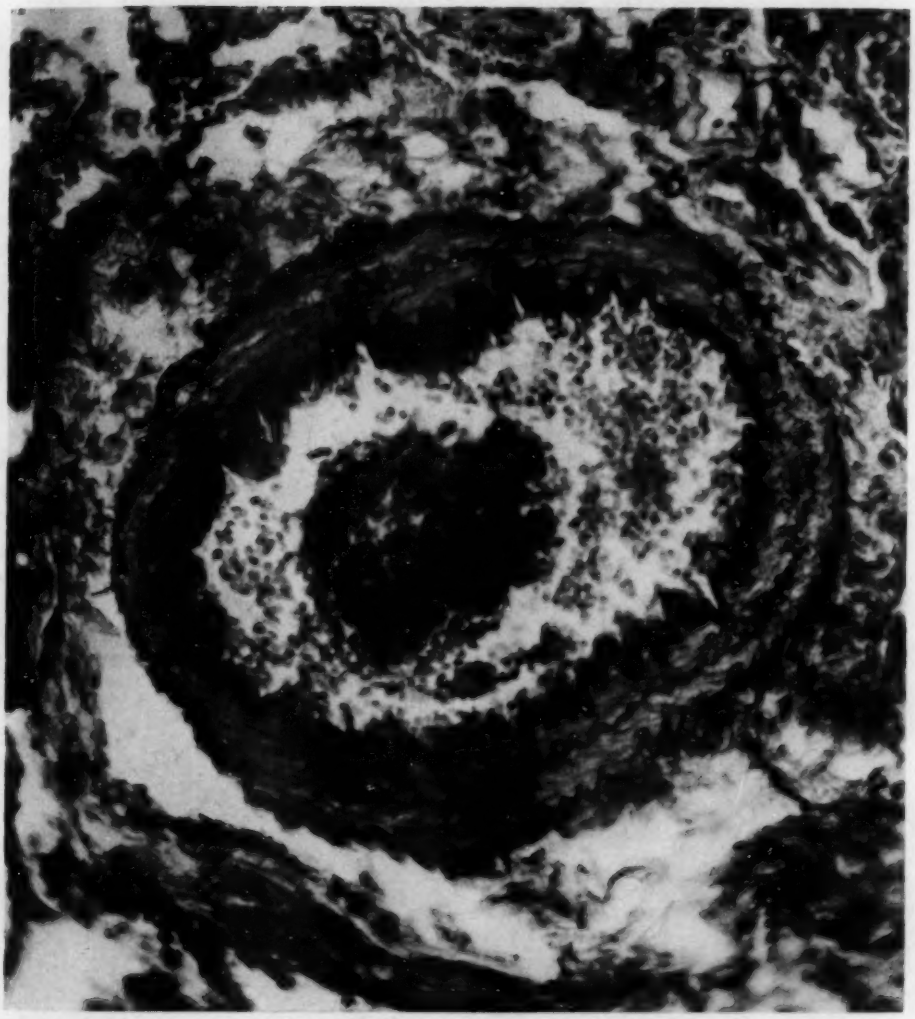

Fig. 3 (case 1).—A pulmonary artery, 0.2 mm. in diameter. The earliest changes which are here noted consist of a thickening of the media due to an increase of elastic fibers and hypertrophy of the muscle fibers. The internal elastic membrane is also thickened. (Weigert's elastic stain; × 500.)

The microscopic picture was that of hypertrophy of the muscle fibers and beginning degeneration, and in the last case large scars were prominent.

Lungs.—Macroscopically, the lungs were moderately collapsed and subcrepitant, and had a dark gray color. Microscopically, the larger bronchi were generally the seat of both mild hyperplastic and degenerative changes. The smaller bronchi usually showed a desquamation of the epithelium. There was no round cell infiltration or peribronchial fibrosis. In the alveoli the underlying pathologic change in all three cases was in the capillaries of the alveolar walls. There were capillary dilatation, capillary contraction and endothelial necrosis. This process, slight in the first case, was far advanced in the third case. Occasionally, anthracotic nodes were situated about small arteries. An interesting observation was that the smaller arteries showing the severest regressive changes were found in the parts of the lung in which the distention of the alveoli was greatest. Further studies are being carried out on emphysematous lungs to determine the significance of this resolution.

Kidneys, Liver and Spleen.—The changes in the kidneys, liver and spleen were similar in the three cases, being those of passive hyperemia. The vessels were slightly sclerotic, but not more than would be expected for the ages of the patients.

Bone-Marrow.—In the bone-marrow, the capillaries were distended by blood with active erythropoiesis and to a less extent granulopoiesis.

PATHOGENESIS

Arteriosclerosis or atherosclerosis (Marchand [6]) has been agreed by most authors to be a physiologic deteriorative process resulting from excessive stress and irritation, chemical, toxic or mechanical (Jores,[27] Marchand;[6] Aschoff [28]). Each portion of the vascular tree suffers in direct proportion to its taxation.

The lung is no longer considered a passive organ in which a simple exchange of gases occurs. Eppinger and Wagner [9] showed the rôle of the lung in the metabolism of lactic acid; Roger and Leon [29] emphasized the rôle of the lung in lipoid metabolism. When one considers also the pulmonary artery with its immense pulmonary tree and its intimate relation to inspired air, gases and foreign bodies, the burden placed on the reticulo-endothelium is at once evident. With increased taxation of

27. Jores, L.: Wesen und Entwickelung der Arteriosklerose, Munich, J. F. Bergmann, 1903.

28. Aschoff: Ueber Entwickelung Wachstum und Alters Vorgänge aus der Gefässen, Jena, Gustav Fischer, 1909.

29. Roger, H., and Leon, Binet: La fonction lipolytique du poumon, Bull. Acad. de méd., Paris **4**:129, 1921.

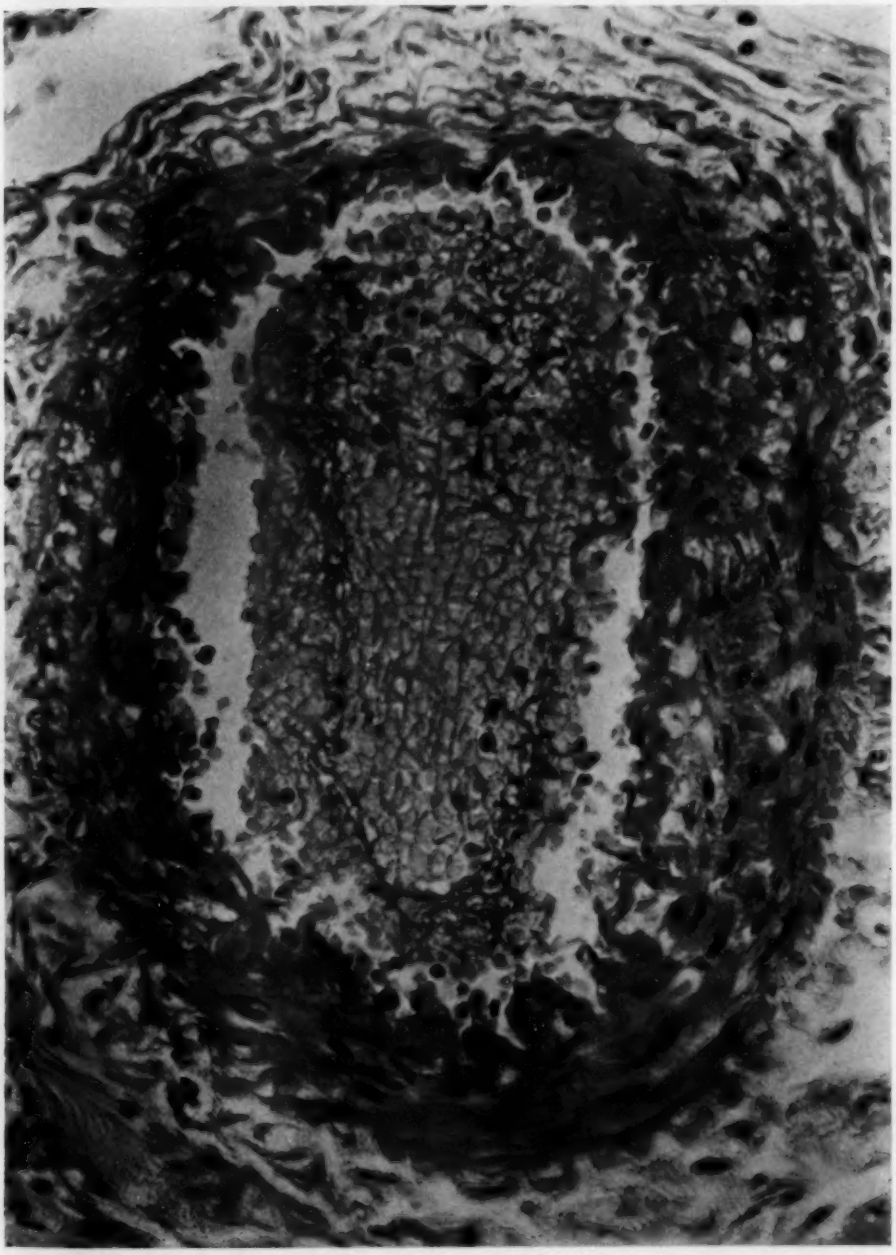

Fig. 4 (case 1).—A pulmonary artery, 0.25 mm. in diameter, showing the earliest degenerative changes in the media. Large vacuoles appear, each having a pyknotic nucleus in its center. The most marked changes are found near the internal elastic membrane. (Hematoxylin and eosin; × 600.)

the lung, be it toxic, chemical or physical, the normal physiologic changes of the pulmonary artery are exaggerated. This process is further hastened by the capillary spasm that results from the irritant, and it terminates in a disappearance of the capillaries and their replacement by fibrous strands in which pyknotic nuclei are evident.

In the cases reported, the patients were all in the descending stage of life, in which additional factors of strain or irritation tended to hasten the physiologic, pathologic process. Because of their occupations their lungs were the seat of the severest stress and suffered accordingly. The constant aspiration of particulate matter (sand, iron particles) or fumes (naptha, benzine, etc.) caused a slight irritation of the bronchi, which probably accounted to a great extent for the cough. These foreign materials (when mixed with mucus) reached the finest ramification of the bronchioles and the alveoli, their passage resulting in a mechanical or chemical irritation of the capillaries which led either to a spasm or to actual necrosis of the endothelium. This process was continually in effect, capillary dilatation coming after capillary spasm. Thus it was noted that areas of capillary hyperemia and areas of capillary collapse with necrosis of the endothelium were sometimes present in the walls of the same alveolus.

Because of this spasm and necrosis of the capillary endothelium, the arterioles and smaller arteries were called on for greater activity. This resulted in hypertrophy of the media of these vessels due to an increase of elastic tissue and a hypertrophy of the muscle fibers. The increase of elastic tissue was associated with a splitting of the internal elastic membrane, which resulted in an increase in the size of the intima.

With the constant increased demand on these arteries, degeneration soon set in. This began in the media adjacent to the internal elastic membrane. The muscle fibers were the first to be involved, and their degeneration was seen as large empty spaces, each having a pyknotic nucleus centrally located. The intima then became involved, but because it lined a canal the process had more room to progress, and thus the intimal proliferation was more marked, sometimes being uniform and obliterating the lumen and at other times nodular. These nodules, in some instances, may have been the result of the organization of thrombi, but in view of their having been rich in fine elastic fibers, the probability is that the majority of them were the result of intimal proliferation.

The same process that took place in the smaller arteries then took place in the larger ones and for the same underlying reason, namely, increased function because of peripheral resistance.

With these changes in the arteries, cyanosis set in because of the lack of oxidation of the blood and because of the stasis of the blood in the peripheral veins due to back pressure. Dyspnea then appeared, per-

haps from mild acidosis and also beginning failure of the heart, especially of its right side. Hemoptysis, which is often described as occurring in this condition, may be explained by rupture of the wall of a vessel as the result of the marked degenerative process that has taken place in the media.

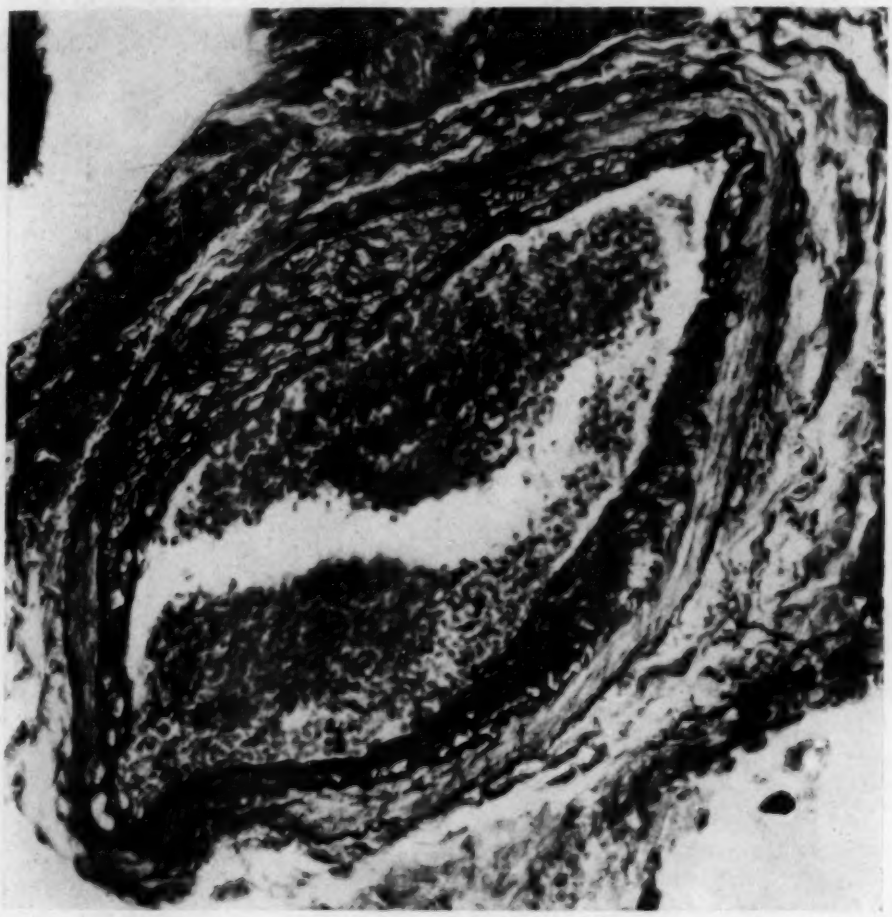

Fig. 5 (case 2).—A pulmonary artery, 0.2 mm. in diameter. The media is reduced in size, and at one point the internal and external elastic membranes approach each other. The internal elastic membrane is split, with a resulting thickening of the intima. (Weigert's elastic stain; × 500.)

At this stage, thrombi are apt to form, for the blood has undergone a chemical change (acidosis) and colloidal change (regressive changes in the body). With the additional factors of stasis and endothelial injury, most marked in the vessels of the lung, thrombi occurred there, affecting both the veins and the arteries.

The narrówing of the lumina of the smaller vessels of the pulmonary artery accounted for the gray, anemic lung, and, because of the resistance offered, resulted in a dilatation of the right side of the heart, which after prolonged taxation became hypertrophied and finally decompensated. Marked passive congestion and edema then made themselves evident clinically.

The passive congestion was also present in the bone-marrow, which caused stimulation of the erythropoietic tissue, and polycythemia resulted.

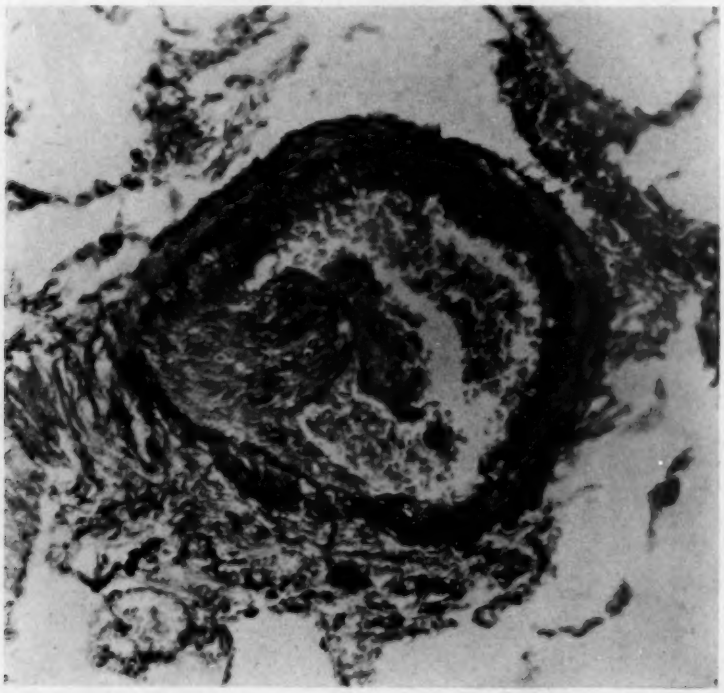

Fig. 6 (case 3).—A pulmonary artery, 0.2 mm. in diameter. The nodular thickening of the intima is the result of an increase of elastic and collagenous fibers. (Weigert's elastic stain.)

After repeated attacks of decompensation, the reserve musculature was exhausted, and the heart failed to compensate. The fact that one patient died with only early evidences of decompensation while another had several such attacks and recovered can best be explained by a poor endowment of muscle reserve or an intercurrent infection that affected this reserve.

Comparative studies carried out on lungs from patients of varying ages who had met with sudden violent deaths revealed a definite but

slight increase in the width of the media of the arterioles and the arteries of the pulmonary artery in persons between 40 and 60 years of age. This was due to thickening of the internal elastic membrane or splitting thereof. The intima was at times also thickened subintimally because

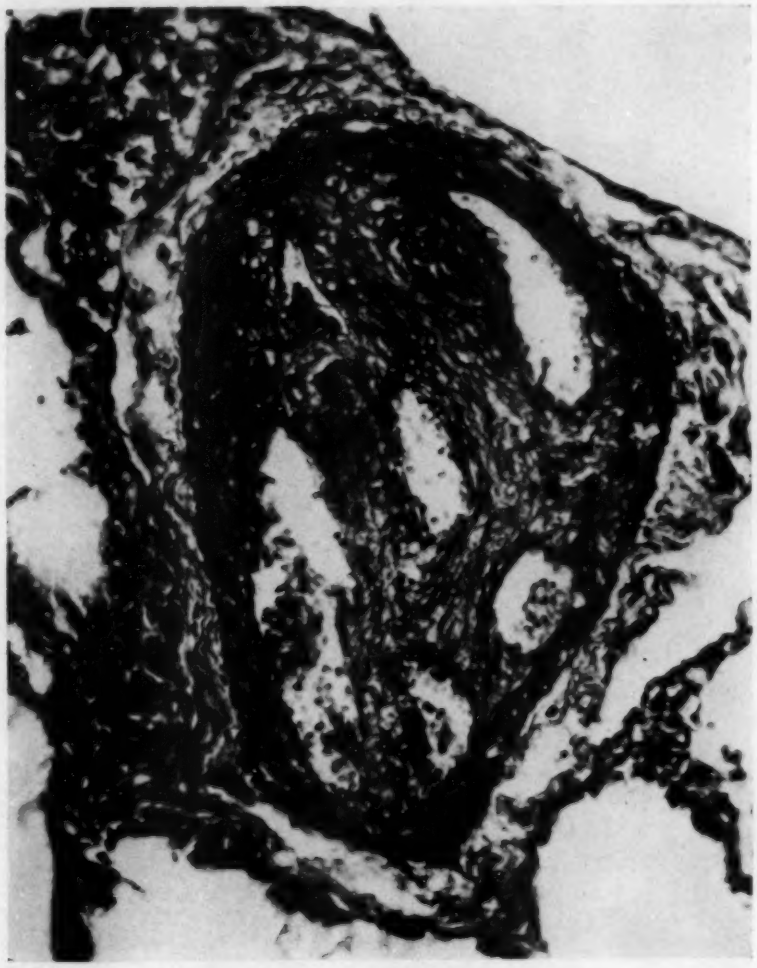

Fig. 7 (case 3).—A pulmonary artery, 0.2 mm. in diameter. The lumen of the vessel has been obliterated and is now canalized. Note the preponderance of elastic fibers in the obliterating mass and the narrow media. (Weigert's elastic stain; × 400.)

of these changes and also because of accumulations of pseudoxanthomatous cells. No evidence of nodule formation, obliteration of lumina or thrombi formation was noted.

The differentiation between the secondary and the primary changes of the pulmonary artery is sometimes difficult. In the secondary form,

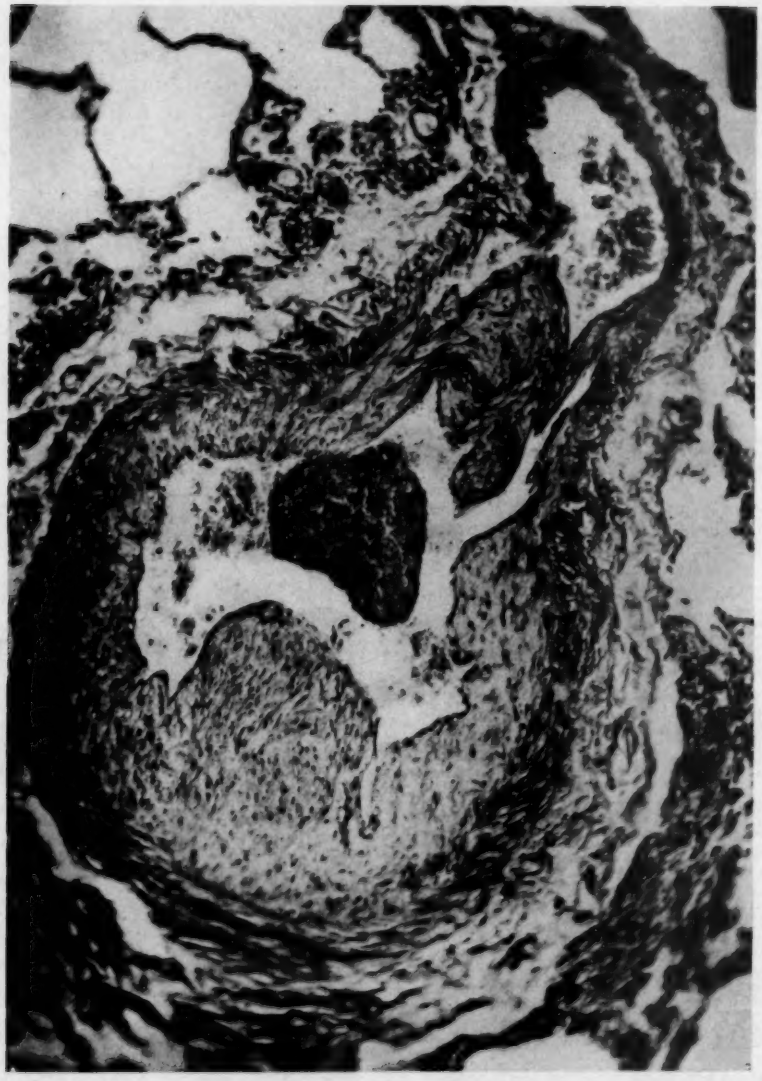

Fig. 8 (case 3).—A pulmonary artery, 0.4 mm. in diameter, showing a nodular thickening of the intima similar to that found in the smaller sized vessels. Note the recent thrombus attached to the intima. (Hematoxylin and eosin; × 250.)

however, the primary lesion is usually found as chronic pneumonia, stenosis of the mitral valve, obliterative pleuritis, etc. Microscopically, the greatest changes are found in the larger branches of the pulmonary artery, whereas the smaller arteries and arterioles may show only slight thickening of the media (Torhorst [30]).

CONCLUSIONS

Pulmonary arteriosclerosis has been defined as a definite clinical and pathologic entity. The basis of this conclusion is found in studies made in three cases in which the various stages of the disease existed. The earliest pathologic changes are in the media of the vessels measuring up to 0.2 mm. in diameter. The process soon extends into the intima and is both proliferative and degenerative. The clinical symptoms are in direct relation to the anatomic changes.

30. Torhorst, H.: Die histologischen Veränderungen bei der Sklerose der Pulmonalarterie, Beitr. z. path. Anat. u. z. allg. Path. **36**:210, 1904.

Laboratory Methods and Technical Notes

A MODIFICATION OF MAC CALLUM'S HEMATOXYLIN METHOD FOR IRON*

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When reliability and simplicity are combined in a technical procedure, the method becomes available for routine purposes and more efficient as a standard in research work. Saving of time and other economic factors are of paramount importance in this sense.

In the original method of MacCallum for the staining of unmasked iron, a freshly prepared 0.5 per cent aqueous solution of hematoxylin was used. When the investigation of such iron compounds was instituted in this laboratory as a part of routine, there was naturally required a fresh solution daily, since the oxidation by the ripening of such a solution occurs within twenty-four hours, and renders it useless for the staining reaction. Experimentation was therefore undertaken to produce a solution that could be used over a length of time in order to spare hematoxylin, to strike out the boresome task of making a new solution daily and to point toward standardization of the method itself. It logically followed that a reducing agent would prevent the natural oxidation of the required solution of hematoxylin. Accordingly, formaldehyde was introduced, and the following method with this slight modification is now presented.

1. Fix tissues in 95 per cent alcohol for five days.

2. Cut on the microtome after embedding in celloidin or paraffin (brain tissue may be cut unembedded as for Nissl's original method).

3. Treat the sections for one hour at 55 C. in nitric acid-alcohol: 4 cc. of nitric acid plus 96 cc. of 95 per cent alcohol.

4. Wash twice in distilled water.

5. Transfer the sections to the hematoxylin solution: 0.5 Gm. of hematoxylin, dissolving by heating in 100 cc. of distilled water, afterward cooling to room temperature, and then adding 1 cc. of Merck's blue label neutral formaldehyde solution. The resulting solution is kept in a tightly stoppered bottle at 55 C. and immediately before use poured into a Stender dish with a ground-glass cover, to prevent the escape of the formaldehyde. At the resulting temperature, the staining reaction occurs almost immediately. The sections, however, should remain in the hematoxylin for five minutes. As a control, a section untreated with the nitric acid-alcohol is placed in the solution with the "unmasked" sections. It will be found that this section does not stain. Under conditions in this laboratory the formaldehyde-hematoxylin solution has been used for three months without losing its ability to combine with the iron. A flocculent precipitate forms within it in a few days; this is removed by filtration. In the course of time another cubic

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centimeter of formaldehyde can be added to replace the theoretical loss of the same substance. The iron of the nuclei stains an intense bluish black owing to the combining of the hematoxylin with the iron salts formed by the previous acid treatment.

6. After washing in distilled water, the sections are transferred to equal parts of ether and absolute alcohol for a differentiation, which removes the excess yellow within the tissue.

7. Follow with neutral xylene and mount in neutral balsam. The preparations are permanent.

The method is useful for the study of the iron content of nuclei. Its application to tumors and to mitoses is especially important. Lately I have combined, or rather superimposed on it, another nuclear stain in the form of a 1 per cent aqueous solution of safranin 0 (Grübler), for the purposes of studying "acid-nuclei" according to Unna, and have found striking "metachromatic" variations of color in cells of different histologic entity and function. Thus, after differentiation in alcohol and ether, the sections are washed in distilled water, stained with the safranin for twenty minutes, rinsed and differentiated in alcohol made acid by the addition of 10 drops of saturated solution of trinitrophenal or of 3 drops of pure hydrochloric acid in 100 cc. of 95 per cent alcohol. The sections are then washed in tap-water, dehydrated quickly with alcohol, cleared in xylene and mounted in neutral balsam.

Hematoxylin thus demonstrates small traces of inorganic iron, and is more sensitive than the prussion blue or ammonium sulphide methods. For purposes of comparison, the iron of nuclei after unmasking with acid may be treated with the usual potassium ferrocyanide or the ammonium sulphide-potassium ferrocyanide procedures. The blue-colored microchemical reactions thus obtained are too faint for accurate comparative study, and possess physical characteristics less suited to ordinary vision and to photomicrography.

General Review

ADDISON'S DISEASE

A STATISTICAL ANALYSIS OF FIVE HUNDRED AND SIXTY-SIX CASES AND A STUDY OF THE PATHOLOGY *

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This paper deals chiefly with a study of 566 cases of Addison's disease reported in the literature from 1900 to 1929, inclusive, with particular emphasis on the pathologic anatomy, the pathogenesis and the correlation of clinical and pathologic data. The material contributed between 1900 and 1929 is chosen as being more reliable for study than cases from the older literature. In addition it affords a comparison with the statistics of Lewin, which were completed in 1892. A study is also made of 29 cases of Addison's disease reports of which were obtained from the protocols of the department of pathology of the University of Minnesota and of Glen Lake Sanatorium.

INCIDENCE

Addison's disease is relatively rare. In 1924, 363 cases were reported in 1,173,990 deaths from all causes in the registration area of the United States. In Minnesota, of the 23,034 deaths in 1924, 9 were due to Addison's disease. The incidence for 1923 corresponds closely to that of 1924. The frequency of the disease for these two years approaches 0.4 per hundred thousand population in the registration area.

It is a common observation that Addison's disease is seldom seen in sanatoriums for tuberculosis. This is probably due to the fact that the extrasuprarenal tuberculous lesions in Addison's disease are usually small and healed or clinically latent. A history of an old tuberculous process occurring many years before the onset of symptoms of Addison's disease is often obtained. It is likely that in many patients treated in sanatoriums the symptoms of Addison's disease develop many years after discharge. There is no doubt that cases of bilateral suprarenal tuberculosis occur in sanatoriums, but it is likely that in many cases the symptoms therefrom are obscured by symptoms of advanced pulmonary tuberculosis, such as weakness, low blood pressure and gastro-intestinal disorders.

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* From the Department of Pathology, University of Minnesota.

AGE

Tuberculosis of the suprarenal glands follows closely the mortality from tuberculosis in general. This is illustrated in figure 1, in which the percentage of the total number of deaths is plotted against five-year age periods. The dotted line represents the age incidence of deaths from tuberculosis of all causes as obtained from the mortality statistics

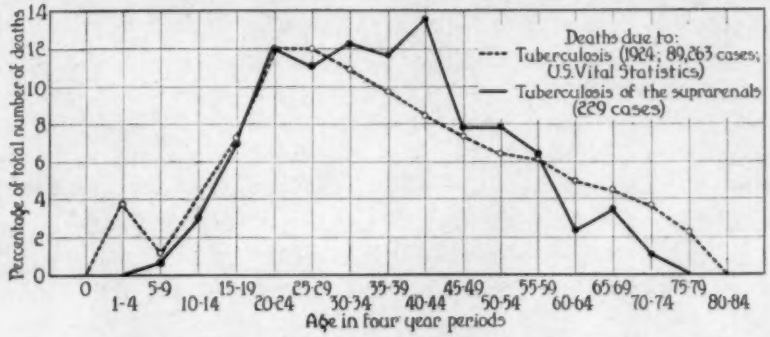

Fig. 1.—Age incidence of deaths from tuberculosis of the suprarenal glands (solid line) and of deaths from tuberculosis of other organs (dotted line).

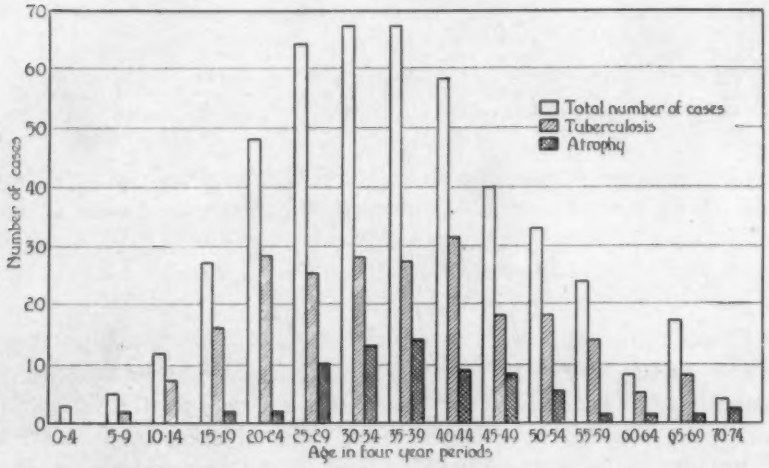

Fig. 2.—Age incidence of deaths from Addison's disease. Comparison of the age incidence of death from atrophy of the suprarenal glands with that of death from tuberculosis of the suprarenal glands.

of the United States. The other line represents the age incidence of deaths from Addison's disease with tuberculosis of the suprarenal glands. The initial rise in childhood is absent in Addison's disease. Both reach a plateau at the thirtieth year. The plateau is much broader in the cases of Addison's disease. The descent in the curve begins at

50 years in the cases of Addison's disease, whereas it begins at the thirtieth year in the cases of death from tuberculosis in general.

In figure 2, the age incidence of 478 cases is given in five-year periods. In 333 of these, the diagnosis was made at autopsy. There are 229 cases of tuberculosis, 66 of atrophy, and 39 of suprarenal lesions of other types. The age distribution of the cases of tuberculosis and of atrophy is also shown in figure 2. The disease is rare in the first years of life; only 3.45 per cent occur in the first decade. The incidence increases rapidly and reaches a maximum in the fourth decade. Following this period, there is a rapid decline in the incidence of the disease. Primary contracted suprarenal glands (atrophy) are rare before the third decade. The maximum number of cases also occurs in the fourth decade of life. The decrease in the incidence is gradual and follows closely the curve of tuberculosis of the suprarenal glands. The mean of the entire number of cases is 36.42 ± 0.41 years (the probable error of the mean used throughout). For primary contracted suprarenal glands, the mean is 37.92 ± 0.83 years; for tuberculosis, 36.87 ± 0.61 years. The difference between the two is 1.05 ± 1.03, which is not significant.

TABLE 1.—*Sex Incidence of Addison's Disease*

	Male		Female	
	Number	Per Cent	Number	Per Cent
Tuberculosis	144	46.00	50	29.07
Primary contracted suprarenal gland	22	7.03	35	20.35
Other cases with autopsy reports	53	16.94	28	16.28
Cases with clinical reports only	94	30.03	59	34.30
Total	313	100.00	172	100.00

SEX

Of the total number of reported cases, 313, or 64.57 per cent, occurred in males, and 172, or 35.43 per cent, in females. The predominance of male over female is evident not only in the reports of cases in which the diagnosis was established at autopsy, but also in the clinical reports (table 1). However, in the case of primary contracted suprarenal glands, the females predominated over the males in the ratio of 1.6 to 1. In the case of tuberculosis of the suprarenal glands, the predominance of males over females, as shown by the postmortem records, can be accounted for partly by the fact that, in most laboratories, there are more postmortem examinations performed on adult males than on adult females. At the University of Minnesota, there are 1.5 times as many on adult males as on adult females; however, in the postmortem reports of tuberculosis of the suprarenal glands the predominance of males over females is 2.88 to 1. The clinical

reports, which are free from this error, show 1.59 males to 1 female. Lewin's statistics [405] give the ratio of male to female as 3.2 to 1.

RACE

Seven cases of Addison's disease in the Negro were reported from 1900 to 1929 (Wahl, Lemann, Goodwin, Evans and Seheult). Increase in depth of pigmentation of the skin and pigment flecks in the mucous membrane of the mouth were noted. The color change is often notable, the patient turning from brown to jet black. Pigmentation of the mucous membrane, an important diagnostic sign in the white race, is of little importance in the colored race, since pigment flecks often occur normally. Because of the difficulty of detecting pigmentary changes in the Negro, it is probable that the disease is more prevalent than one is led to believe by the case reports. Busch reported a case in a mulatto. Reports of Addison's disease in Jews are rare. Statistics are not available for the yellow races. Numerous case reports indicate that it occurs in the Japanese (Sakaguchi, Hayashi and Katayama; Gyotoku and Momose).

HEREDITY

Proved cases of Addison's disease in more than one member of a family are exceedingly rare. Fahr and Reiche reported symptoms of Addison's disease in three brothers of a family of twenty-three, eleven of whom died in youth. One, 23 years of age, was examined post mortem. Atrophy of the suprarenal glands was found. The other two showed marked pigmentation of the skin and weakness. Flemming and Miller described a case of undoubted Addison's disease in a woman who had four children with symptoms of weakness, brownish pigmentation of the skin and occasional attacks of diarrhea. Unfortunately, further information as to the duration of these cases cannot be found in the literature, and it is impossible to state with certainty that these were true cases of Addison's disease. Croom described a case in a girl, aged 9, who had two sisters, aged 6 and 3½, who had pigmentation of the skin and listlessness. Pigmentation of the mucous membrane of the mouth was present only in the girl, aged 9. In Green's case, the history was obtained that one sister died of a similar malady. Pigmentation of the skin of some other member of the family was noted in the cases reported by Bittorf, Boenheim, Cattermole, Aslan, Wakefield and Smith, and Richon. These cases are questionable, as insufficient data are at hand to establish the diagnosis with certainty. Bittorf cited Saundby's case as the only proved case of Addison's disease in more than one member of a family. Lewin in his entire study found three cases in which the disease had been considered hereditary (the cases of Bell, Espagnes and Feuerstein).

It is doubtful, therefore, whether heredity plays an important rôle in the genesis of the disease, although it cannot be denied that in rare instances there is an hereditary tendency. Bauer believed that a constitutional predisposition may be a hereditary factor in this disease, but that other intercurrent factors are necessary before the disease results.

PATHOLOGIC ANATOMY AND PATHOGENESIS

CLASSIFICATION AND FREQUENCY OF LESIONS IN THE SUPRARENAL GLANDS IN ADDISON'S DISEASE

There are 566 cases available for study. The authors of these reports are given in the bibliography which is arranged so as to cor-

TABLE 2.—*Classification and Frequency of Lesions in the Suprarenal Glands in Addison's Disease*

Lesions	Cases	Per Cent
Inflammatory changes		
Tuberculosis		
Bilateral	244	60.54
Probable bilateral	33	8.18
Unilateral	4	1.00
Total	281	69.72
Pyogenic infection	2	0.50
Syphilis	1	0.25
Degenerative changes		
Primary contracted suprarenal gland (atrophy)	65	16.13
Probable atrophy	13	3.25
Amyloidosis	7	1.73
Fatty degeneration	2	0.50
Neoplasms		
Primary	2	0.50
Metastatic	3	0.74
Vascular lesions		
Venous thrombosis	3	0.74
Arterial emboli	1	0.25
Hemorrhage	1	0.25
Miscellaneous lesions		
Trauma	2	0.50
Metaplasia of bone-marrow	1	0.25
Bilateral aplasia	2	0.50
Pressure atrophy	2	0.50
Hypoplasia	1	0.25
Undeterminable nature	10	2.48
Addison's disease without lesions in the suprarenal glands	4 (?)	0.99 (?)
Total	403	100.00
Cases of Addison's disease on which clinical reports only are available	163	
Total number of cases	566	

respond to the foregoing classification. In addition, a list of references is given of reports that I could not obtain.

In 402 cases, the autopsy reports are given. These are classified according to the pathologic changes in the suprarenal glands.

The number and percentage of the various diseases recorded in the literature of the last thirty years are given.

Tuberculosis of the suprarenal glands is the most frequent cause of Addison's disease. The percentage of cases in the recent literature

is 60.55. Lewin reported 95 of 272 typical cases, or 35 per cent, in which the lesion was considered to be tuberculous. Primary contracted suprarenal gland (atrophy) occupies second place, with 65 cases (16.13 per cent), whereas in Lewin's early statistics[466] there are 25, or 8.4 per cent. The relative frequency of occurrence of the disease in recent years as judged by the literature is probably too high, owing to increasing interest in this condition in recent years. A case of atrophy is more apt to be reported than one of tuberculosis. The frequency of primary contracted suprarenal gland in recent individual statistics is as follows: Barker, 3 cases of 28 at the Mayo Clinic; University of Minnesota, 4 cases of 29 coming to autopsy; Conybeare and Millis, 8 cases of 29 at Guy's Hospital. Other forms of degenerative change include amyloid disease, 7 cases; fatty degeneration, 2 cases. Neoplasm as a cause of Addison's disease is exceedingly uncommon; only 5 cases are reported in the recent literature. Lewin found only 9 typical cases, or 3.3 per cent. Vascular lesions consist of venous thrombosis, 3 cases; arterial emboli, 1 case; hemorrhage, 1 case. In the fifth group there are 2 cases of trauma; 1 case of metaplasia of the bone marrow, 1 case of hypoplasia, 2 cases of pressure atrophy and 8 cases of undeterminable nature.

In the sixth group there are 4 questionable cases of Addison's disease without lesions in the suprarenals (see page 773). This is in marked contrast with the frequently quoted number placed in this category by Lewin. In his first group of statistics there are 28 cases of a total of 311 in which the suprarenal glands are intact. In his second group of statistics, the suprarenal glands are stated to be normal in 8 per cent of 561 cases. Of the total, Lewin gives 12 per cent normal and 88 per cent diseased.

It is clearly evident that, in the older cases, Addison's disease was confused with many other conditions producing pigmentation of the skin, principally vagabond's disease acanthosis nigricans, pellagra, bronze diabetes, sprue, pernicious anemia and ochronosis, which are now better understood. It is also probable, as pointed out by Furuta, that the suprarenal glands, diagnosed grossly as normal, may have been the site of marked destructive changes.

From a review of the literature of the last thirty years, it is evident that Addison's disease is almost invariably accompanied by destructive lesions in both suprarenal glands. These lesions are of many types, but most frequently are tuberculous. This is in accord with Lewin, but opposed to the unitarian point of view of Wilks, Greenhow, and Bramwell,[428] who held that the disease is due to a peculiar fibrocaseous degeneration of the suprarenal glands. There is also no support of the neo-unitarian point of view of recent writers, Kovacs and Omelskyj,

who stated that they do not regard primary contracted suprarenal gland (their cytotoxic contracted suprarenal gland) as a true form of Addison's disease (this will be discussed in the last part of this article, which will be published in the December issue of the ARCHIVES, and will appear under the heading *Relation of Blood Pressure to the Relative Degrees of Destruction of Cortex and Medulla in Suprarenal Tuberculosis and Primary Contracted Suprarenal Gland*).

TABLE 3.—*Distribution of Tuberculosis in Tissues Other Than the Suprarenal Glands*

	Cases
Lungs	
Healed scars	36
Recently acquired active lesions	7
Limited active tuberculosis	40
Extensive chronic tuberculosis	19
Extent of lesions undeterminable	22
Total	124
Pleura	
Bilateral adhesive pleuritis	14
Unilateral adhesive pleuritis	7
Degree undeterminable	24
Disseminated miliary tuberculosis	16
Genito-urinary tract	
Kidneys	
Left kidney	3
Right kidney	7
Bilateral involvement	12
Prostate	5
Epididymis	7
Uterus	1
Uterine tube	3
Lymph nodes	
Bronchial and mediastinal	29
Mesenteric	4
Retroperitoneal	14
Other nodes	7
Other organs	
Pericardium	2
Peritoneum	8
Joints	5
Bones	9
Intestines	7
Thyroid	2
Liver	11
Spleen	7
Total	51

TUBERCULOSIS

Frequency of Primary Tuberculosis of the Suprarenal Glands.—The impression is obtained from the older literature that tuberculosis of the suprarenal gland is often a primary infection. In an extensive review of cases collected from the literature, Lewin found primary involvement in 132, or 26.4 per cent. Elsässer in 1906 collected 549 cases of tuberculosis of the suprarenal glands and found 5 cases that were certainly primary, 62 that were very probably primary and 29 that were doubtful.

The distribution of tuberculous lesions elsewhere in the body in 243 cases of tuberculosis of the suprarenal glands is given in table 3.

In only nineteen cases are the lungs reported normal, and in only seven cases are there no lesions elsewhere than in the suprarenal glands. These observations agree well with those of Schwarz [497] who, in a study of sixty-five cases of tuberculosis of the suprarenal glands, found tuberculous lesions of the lung of the same age or older in every case. This unusually high incidence is probably accounted for by the painstaking search for tuberculous foci made in Ghon's laboratory. In the cases reviewed in the literature, a history of exposure to infection is not infrequent. A history of tuberculosis in one or both parents was obtained in thirteen cases; in a brother or sister, in sixteen cases; in

TABLE 4.—*The Clinical Relation of Tuberculosis to Addison's Disease*

	Cases
A history of tuberculosis from which complete recovery was made	
Tuberculosis of lung	8
Tuberculosis of lymph nodes	7
Tuberculous pleurisy	10
Bone tuberculosis	3
Joint tuberculosis	3
A history of tuberculosis before the onset of Addison's disease (tuberculosis still active at time of onset)	
Tuberculosis of lung	13
Tuberculosis of lymph nodes	3
Bone tuberculosis	4
Joint tuberculosis	3
Tuberculosis of kidney	1
Pleurisy	2
No history of previous infection	27
Clinical evidence of tuberculosis during the course of the disease	
Lung	
Slight or moderate activity	50
Marked activity	10
Activity indeterminate	9
No evidence of activity	31
Other organs	
Epididymis	2
Bone tuberculosis	34
Tuberculosis of lymph nodes	5
Tuberculosis of prostate	1
Tuberculosis of kidney	1
Fistulas	2
Intestinal tuberculosis	1

near relatives to whom the patients were exposed, in eleven cases. The clinical relation of tuberculosis to Addison's disease is shown in table 4.

These observations are important in that they emphasize that tuberculosis of the suprarenal glands is seldom, if ever, a primary infection. In the majority of cases, however, the extrasuprarenal lesions are not extensive and are clinically latent.

Routes of Infection.—Three possible routes of infection of the suprarenal glands have been considered by various authors, viz., intrauterine, hematogenous and lymphogenous. Elsässer concluded that, in cases of isolated suprarenal tuberculosis, the infection must find its explanation in a congenital infection followed by a long period of latency. There is much evidence opposed to this theory. Although it is well known that bacilli may be present in the blood stream and tissues without producing tissue reaction, it is highly improbable that the bac-

teria remain latent for many years. The low immunity of the tissues of infants furnishes a fertile field for the development of bacilli, and infections in the fetus would not be long in becoming disseminated. That tuberculosis is rarely transmitted through the placenta is indicated by the rarity of reports of such cases. Hübschmann [454] was of the opinion that transmission via placenta is usually accompanied by tuberculosis of that tissue. He considered only those cases congenitally transmitted in which the symptoms of the disease occur shortly after birth, rarely later than the third week of life. Schmorl's case of bilateral extensive fibrocaseous tuberculosis in an infant of 12 days is an example of congenital infection, and also illustrates the rapidity of the lesion in the new-born infant.

There is little evidence in the observations at necropsy that infection takes place via lymphatic channels. Involvement of adjacent lymph nodes is not infrequent, and may be considered as an extension from the lesion in the suprarenal gland. The position of the primary lesion in the majority of cases is such that extension through lymphatic vessels is improbable.

The anatomic relationship of lesions in the lung and lesions in the suprarenal gland strongly suggests the hematogenous route. Schwarz,[497] in a study of sixty-five cases of tuberculosis of the suprarenal glands, both unilateral and bilateral, found lesions of the same age or older in the lungs in every case. In almost half of his cases the lungs were the only other organs involved. The remainder showed hematogenous involvement of other viscera. Schwarz concluded that the suprarenal infection is secondary to lesions in the lung and that the infection is carried by the blood stream. It has been pointed out that, in Addison's disease, the lesion is seldom primary, and that it is associated in most cases with active lesions elsewhere in the body. There are cases, however, in which the primary lesion is healed, and a small number in which no lesions can be found outside the suprarenal glands. These cases have led many to regard the infection as congenital or hereditary. However, in the light of recent knowledge of tuberculosis, this assumption is unnecessary. Lubarsch, Rabinowitsch and others have shown that apparently healed foci may harbor the bacilli. Hübschmann [454] also held that these areas are capable of giving off bacteria into the blood stream without local acute exacerbation of the lesion. Also Löwenstein showed that bacillemia may occur in patients harboring lesions that anatomically are difficult to find. Such hidden foci in parts of the body other than the lung, in many of these cases, must be considered. It is also possible that extensive bilateral lesions in the suprarenal glands may produce a state of immunity in the rest of the body, so that lesions elsewhere tend to remain localized and to heal. The frequent association of hematogenous infection of other viscera, such as the spleen,

kidney, liver, epididymis, etc., also is strong evidence favoring a hematogenous origin of the lesion in the suprarenal glands.

Predisposition and Susceptibility of Suprarenal Glands to Tuberculosis.—Tuberculosis of the suprarenal glands is much less frequent than tuberculosis of many other organs. Hübschmann [454] gave the frequency of tuberculosis of other organs in association with pulmonary tuberculosis as follows: urogenital system, 62 per cent; bones and joints, 30 per cent; intestines, 7 per cent; suprarenal glands, 2 per cent, and skin, 2 per cent. The frequency of tuberculosis of the suprarenal glands found by other authors is higher. Schwarz [497] found 85 cases, or 3.1 per cent, in a series of 2,700 cases of tuberculosis. Ophüls found the suprarenal glands involved in 5 per cent of his cases. At the University of Minnesota, of 1,050 cases of tuberculosis, 51, or 4.85 per cent, showed tuberculosis of the suprarenal glands.

A number of hypotheses have been advanced to explain the occurrence of extensive, apparently isolated, bilateral tuberculosis of the suprarenal glands found in Addison's disease. Wiesel,[517] Neusser and Wiesel, Hedinger, Löffler and others held that the suprarenal glands are predisposed to infection by a hypoplastic condition of the chromaffin system which is associated with status lymphaticus. Bauer cited an analogous situation in which hypoplastic organs are the site of tuberculosis, but such reports are few compared with the frequency of hypoplasia. Schür was opposed to the belief that a developmental hypoplasia predisposes an organ to disease.

The inconstancy of lymphatic and thymic hyperplasia in cases of tuberculosis of the suprarenal glands (see page 774) also throws doubt on the etiologic significance of status lymphaticus. Löwenthal recently pointed out the meagerness of evidence on which Wiesel based his conclusion that chromaffin tissue is hypoplastic in his so-called cases of status lymphaticus. In the majority of cases of primary contracted suprarenal gland, the medullary tissue shows little or no deviation from the normal, the cortex being the main site of the lesion.

Hansemann regarded the local predisposition of the suprarenal gland to tuberculosis as the result of a low fat content of the tissues. Schür considered that the suprarenal glands are made more susceptible to infection by injury as a result of a previous acute infectious disease.

While it is a common observation that a patient dates his first symptom to an attack of influenza, of grip or, less frequently, of typhoid fever, of diphtheria, etc., it is improbable that these diseases predispose the suprarenal gland to tuberculosis. The influenza epidemic of 1918, 1919 and 1920 had no appreciable effect on the mortality rate of Addison's disease as given in the mortality statistics of the United States (fig. 3).

The slight yearly increase in the mortality rate of Addison's disease is apparent before the 1918 epidemic and parallels the increase of reported deaths from all causes.

Infectious diseases, particularly acute infections of the upper part of the respiratory tract, however, may bring about an acute exacerbation of a preexisting tuberculous lesion, as a result of which a latent process may become clinically manifest, or, if symptoms are present, they become more pronounced. Also, these effects may be produced in another manner. Dietrich and Siegmund, Wülfung, Goldzieher, Thomas and others showed that acute infectious diseases are frequently the cause of marked degenerative changes in the cortex of the suprarenal gland. It is probable that the surviving cortical tissue of a tuberculous

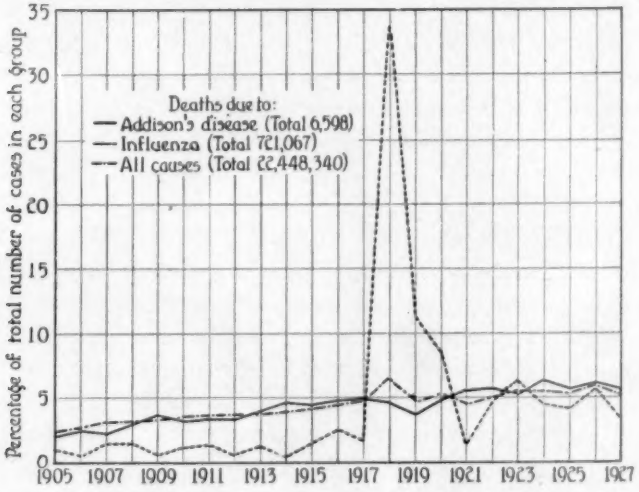

Fig. 3.—Comparison of incidence of death from Addison's disease with that of death from influenza.

gland may be injured by an acute infectious process elsewhere in the body.

Löwenstein held that infection of one organ of a pair leads to susceptibility to infection of the other. In a study of clinical records at a hospital in Vienna, he found that the organic system in which the first metastasis is established is also a frequent site of subsequent metastases. Thus, tuberculosis of the eye is first unilateral and later becomes bilateral. Renal tuberculosis is usually unilateral in the early stages and bilateral in the later stages. He believed that the same applied to the suprarenal glands. To explain this phenomenon, he added that tissue destroyed during the tuberculous process serves as an antigen for the production of specific antibodies ("resorbins") which exert an injurious effect on analogous structures and render them more susceptible to subsequent infection. Sumiyoshi found in guinea-pigs that infection of

one organ often leads to involvement of the opposite organ. Further experimental confirmation of these views is not at hand.

From an analysis of forty-nine cases of tuberculosis of the suprarenal glands, there is evidence that the infection is first unilateral and later bilateral. It is found that unilateral lesions are seldom extensive and but rarely destroy the entire gland. When bilateral, one gland often shows more recent and less extensive involvement than the opposite organ. It seems, therefore, that the same conditions apply here as in the kidney and the eye. The exact mechanism of the predisposition, however, is not yet clear.

TABLE 5.—*Degree of Destruction of Suprarenal Glands in Cases of Tuberculosis of the Glands from the Department of Pathology of the University of Minnesota and Glen Lake Sanatorium*

	Partial Destruction		Complete Destruction	
	Right	Left	Right	Left
Unilateral lesions	4	8	2	0
Bilateral lesions without symptoms	2	3	4	3
Bilateral lesions with symptoms	7	4	17	18

TABLE 6.—*Degree of Destruction of Suprarenal Gland in Cases of Tuberculosis of the Glands as Recorded in the Literature*

Gross appearance of the suprarenal glands	Cases
Total destruction of both	72
Complete destruction of right; left incompletely destroyed	6
Complete destruction of left; right incompletely destroyed	8
Normal tissue recognizable in both	9
Microscopic appearance	
Rests of normal cortex	39
Small cortical adenomas	27
Normal medulla	1
No normal tissue	16

The extensive alterative and exudative change in the glands is strongly suggestive that the inflammation is allergic. It is probable that this allergic state is the result of the sensitization of one organ to the tubercle bacillus or its products as the result of a previous primary infection of the opposite organ.

Structural Changes in the Suprarenal Glands in Tuberculosis.—In addition to a review of case reports, a study was made of fifty-one cases of tuberculosis of the suprarenal glands as recorded in the Department of Pathology at the University of Minnesota and in Glen Lake Sanatorium. Of these cases, fifteen showed unilateral tuberculosis, and in these symptoms of Addison's disease were absent. Of the thirty-six cases that showed bilateral tuberculosis, twenty-five gave clinical signs of Addison's disease; six were clinically latent, and in five the diagnosis could not be made because of insufficient clinical data. Table 5 shows the degree of destruction of the organ in these cases. In the cases

obtained from the literature, the degree of involvement of the suprarenal gland is determined to be as shown in table 6.

In unilateral tuberculosis, the destruction of the organ is seldom complete. As a rule, the lesion consists of one or more caseous nodules, single or confluent. There is no predilection for cortex or medulla. The lesion may occupy a pole of the gland and cause a nodular swelling. Nodules in the cortex tend to be isolated and well delimited; those in the medulla tend toward confluence. Destruction of the gland in cases of bilateral tuberculosis without symptoms is not as complete as in those with symptoms, although there are a few cases in the former group in which no suprarenal structures are recognizable grossly. Macroscopically recognizable tissue in cases with clinical symptoms of Addison's disease was found seven times in the right and four times in the left suprarenal gland. In the remaining cases, no macroscopic suprarenal tissue was seen. The exact amount of remaining tissue cannot be estimated from this study because of the marked distortion of the normal markings and the irregular distribution of the surviving tissue.

The approximate size of the organs in tuberculosis of the suprarenal glands is as follows: both enlarged in eighty-three cases; both normal size in ten cases; one normal and one large in four cases; one large and one small in seventeen cases, and both smaller than normal in eight cases.

In thirty-one cases, the weight of the left gland is given and in thirty-two cases the weight of the right gland. The mean weight of the right gland is 11.72 ± 5.07 Gm.; the mean weight of the left is 13.98 ± 5.62 Gm. The maximum weight is 45 Gm.; the minimum weight is 4.1 Gm. The normal weight of the suprarenal gland in a man is 11.2 Gm., and in a woman 10.6 Gm. (Scheel).

The organs are firm, nodular, and of a mottled grayish-red color. The triangular wedge-shaped appearance may be maintained in the presence of extensive lesions. The capsule is thickened and adherent to the surrounding tissues. Fusion with the stomach, liver and kidney is described.

In the majority of cases, the substance is replaced completely by semiconfluent caseous nodules, varying in size from a few millimeters to 2 or 3 cm. in diameter, separated by septums of grayish-white connective tissue. Between the caseous nodules, a tissue of reddish-brown color with fine, grayish nodules is often present. Microscopic sections through these areas often show active miliary tubercles. Conversion of the entire gland into a shell containing soft, cheesy or semifluid contents is described. Normal tissue is usually present in the form of a thin rim of yellow cortical substance, or a portion of intact medulla and cortex may be present at one or more poles of the glands. In a small

number of cases one or both glands may be shrunken. The substance is composed of a thick layer, often stratified layers, of connective tissue enclosing firm, inspissated, yellow, caseous, partially calcareous nodules. Suprarenal tissue cannot be identified grossly. This form is designated by Dietrich and Siegmund as "indurende (fibröse) Tuberkulose." This is not an independent form of tuberculosis of the suprarenal glands, but represents an older stage; transitions from the larger caseous forms to the small indurated forms may be seen.

Microscopically, the glands are replaced for the most part by large homogeneous confluent caseous masses. The reaction about these varies considerably. Most commonly, areas of caseation are well walled off by a thin zone of connective tissue containing abundant collagenous fibrils and poor in nuclei. In other portions of the same gland, the process may be more active, the reaction consisting of marked epithelioid cell formation, giant cells and wide zones of lymphocytic infiltration. Less frequently, the proliferative reaction is lacking, and wide areas of caseation are bordered by partially necrotic parenchyma and leukocytes.

TABLE 7.—*Activity of the Lesion in Tuberculosis of the Suprarenal Glands*

	Acute	Chronic	Both Chronic and Acute	Healed
Unilateral lesions	8	2	2	0
Bilateral lesions without symptoms	1	1	3	0
Bilateral lesions with symptoms	1	3	13	1

In glands that grossly appear healed, areas may be obtained that show marked activity in the form of dense clusters of miliary tubercles. Both proliferative and caseous types are seen in about equal frequency. The smaller glands are not infrequently the site of widespread fibrosis, and only an occasional area of caseation or of giant cells distinguishes the lesion. Hübschmann [454] described acute exacerbation of apparently healed foci in which there is an extension of the process into uninvolved portions of the suprarenal gland. The connective tissue wall may be broken down and included in the caseous mass. These exacerbations may be repeated several times until the entire suprarenal gland is destroyed. In table 7, the activity of the lesion in thirty-four cases studied microscopically is given.

In the unilateral lesions, the process appears more active than in the bilateral ones. A wide acute caseous form involving both suprarenal glands is rarely observed in Addison's disease. In the majority of cases, the process is chronic, with areas of acute exacerbation. Complete healing is rarely observed. Complete quiescence of the lesions was present in only one case. No proved case of healed tuberculosis of the suprarenal glands has been reported in the literature. Kovacs reported a case in a woman, aged 27 years, in which the organs were

very small and showed a central area of calcification and bone formation, but he was not certain that it was tuberculous. Calcification is not uncommonly seen. Bone formation has been described.

In both unilateral and bilateral lesions, the medulla is frequently completely destroyed, whereas large portions of the cortex may remain. This indicates that the medulla is less resistant to the infection than the cortex. This is also clearly shown in the experiments on dogs by de Vecchi. By injecting virulent tubercle bacilli into the adrenal glands, he was able to show that the medulla was first completely destroyed, and that then the process slowly involved the cortex, which appeared more resistant to the infection than the medulla. Small nodules of

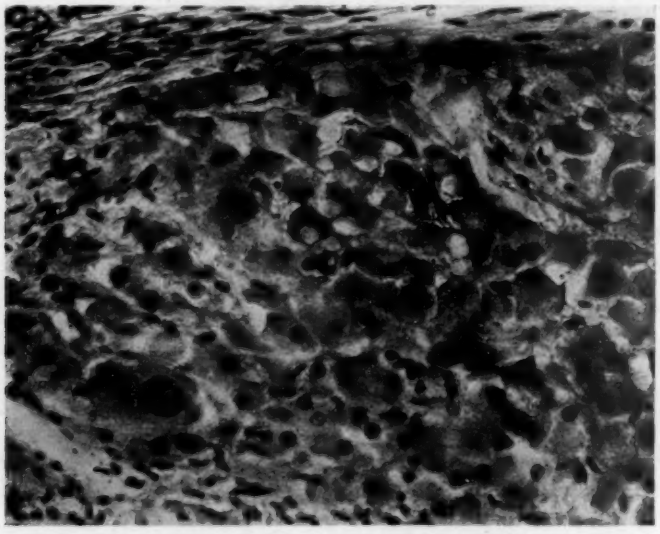

Fig. 4.—Edge of a small circumscribed area of hyperplastic cortical cells in a case of tuberculosis of the suprarenal glands.

cortical tissue may become separated by connective tissue bands. These have the structure of zona fasciculata and often show marked degenerative changes. Not infrequently small nodules of cortical cells are present near the periphery of the gland and occasionally in the fibrous capsule which are identical in structure with the hyperplastic nodule so frequently seen in atrophy of the suprarenal glands (fig. 4). In the more acute lesions, the cortical remains often show marked degenerative changes in the form of swelling of the cells, vascular degeneration, karyorrhexis or karyolysis of the nuclei.

Fibrosis of the capsule and the surrounding tissue may be extensive. Included in the fibrous mass may be seen sympathetic nerves, blood vessels and small groups of sympathetic ganglions. Hyperplastic inti-

mal changes in the smaller arteries are common. The veins are not infrequently the site of thromboses.

Tubercle bacilli were found in thirteen of twenty-nine cases stained by the Ziehl-Neelsen method. The cases in which results were negative were those in which organs had been preserved for many years in 10 per cent formaldehyde. Barker reported the finding of tubercle bacilli in eleven of twenty-five cases examined at the Mayo Clinic. In the literature, reports of finding tubercle bacilli in smears and in sections are given in thirty-one additional cases.

SYPHILIS

Syphilis of the suprarenal glands with symptoms of Addison's disease was present in only one case proved at autopsy (Sézary). In this case, symptoms of asthenia and pigmentation followed shortly after primary infection, and death occurred four months later. The suprarenal gland showed sclerosis and gumma formation. Spirochetes were demonstrated. Clinical reports are more numerous. Wile, Schaffner and Howard, Gaucher and Gougerot and others described cases that were believed to be due to syphilis. The diagnoses were based on the favorable response of these patients to antisyphilitic treatment. Since spontaneous remissions are often seen in cases of Addison's disease, the response to antisyphilitic treatment cannot be accepted as adequate proof of the syphilitic nature of the lesion.

The infrequency of autopsy reports of syphilis and the prevalence of clinical cases raise the question whether some cases diagnosed anatomically as tuberculosis may not be syphilitic. Demonstration of the tubercle bacillus is not frequently made. In cases with widespread fibrosis and extensive lymphocytic infiltration, it is difficult to rule out syphilis on microscopic structure. The evidence that these cases are not syphilitic is strongly suggestive, but not conclusive. Careful search will often show tubercle bacilli in cases in which the lesion is suggestive of syphilis. A history of syphilis or of organic lesions suggesting syphilis is reported in only three cases. Congenital syphilis of the suprarenal gland is not infrequent and may result in the formation of interstitial fibrosis, miliary gumma (Guleke, Gierke) and rarely large central necrosis and granulation tissue. Simmonds[498] found a perisuprarenalitis in congenital syphilis, but did not find it in the adult. Winogradow found on examination of a large number of cases of visceral syphilis that gummas of the suprarenal gland were absent. It is highly questionable, therefore, that syphilis plays an etiologic rôle in cases of fibrocaseous destruction of the suprarenal glands, in which the etiologic agent is not demonstrated.

PRIMARY CONTRACTED SUPRARENAL GLAND (ATROPHY)

This condition has been designated by many names. Bittorf (1908), in his monograph on Addison's disease, collected a group of cases under the heading of chronic idiopathic (primary) suprarenal insufficiency (cirrhosis, atrophy). It has been variously termed "reine" atrophy (Bloch), "einfache" atrophy (Karakascheff), idiopathic atrophy (Simmonds), chronic dystrophy (Kiefer), inflammatory granular atrophy (Rössle), cytotoxic contracted suprarenal gland (Kovacs), cirrhosis (Lampl, Lucksch) and hypoplasia (Hedinger, Kraus). The condition is not a simple atrophy in the restricted sense of the term, since the organ does not shrink because of atrophy of its cellular elements, but because of necrosis and disappearance of cells. Rössle suggested granular atrophy, because of the marked inflammatory reaction of a hemorrhagic nature seen in his case. This case, however, differs from the others in the degree of inflammatory reaction secondary to the degenerative changes in the parenchyma. The term hypoplasia is erroneous, as the disease is acquired. The expression "cirrhosis" of the suprarenal gland, suggested by Lucksch and Lampl, may fit individual cases in which the growth of the reticulum is marked. These cases are few, and there are transitions from those with marked, to those with little or no, connective tissue reaction. Recently Kovacs suggested the term cytotoxic contracted suprarenal gland. This descriptive term is based on the unwarranted assumption that the disease is due to a circulating toxin that injures and destroys the cells of the suprarenal cortex. Unless there is some evidence to support this view, this term should not be used.

The term "primary contracted suprarenal gland" is here adopted to include all of these cases, since there is little known of the etiology and since the fibrosis consists mainly of a collapse of the reticulum following degenerative changes in the parenchyma.

Frequency.—It is a rare disease. The older reports have been collected by Simmonds (1904), who studied twenty-four cases, and later by Bittorf (1908), who collected forty-seven cases. Since 1900, sixty-eight cases have been reported, or 16.13 per cent of all the cases that came to autopsy. It has already been mentioned that this does not represent the relative frequency of primary contracted suprarenal gland, because recently, owing to increased interest in the disease, there is more tendency to report cases of atrophy than cases of tuberculosis.

Classification.—Bittorf has separated his cases into two distinct groups, simple atrophy and inflammatory atrophy, or cirrhosis, of the suprarenal gland. Simple atrophy is characterized by a small thin organ. One suprarenal gland may be more affected than the other. Inflammatory changes are lacking, and there is no increase of connective

tissue. The cortex is lacking in one or more layers, or there may be alteration of the parenchyma in the form of fatty degeneration, decrease in fats and, less frequently, necrosis. In the inflammatory type, there is often adhesion to the surrounding tissue and a thickening of the capsule, trabeculae and blood vessels. Degenerative changes are marked and are accompanied by marked round cell and polymorphonuclear cell infiltration. In an analysis of the cases collected from the literature and my own cases, given in later paragraphs, it is found that a sharp separation of the cases into these two groups of Bittorf cannot be made. Cases that conform in all details to the two groups are few in number, whereas the majority show characteristics of both groups. Sections taken from various portions of one organ may show in places little or no reaction of the reticulum, but a simple disappearance of the cortical cells, leaving the collapsed supporting reticulum and a moderate lymphocytic infiltration; while in other places there may be active proliferation of the connective tissue, a marked cellular reaction and thickening of the capsule (see page 765 and fig. 9). The degree of reaction of the connective tissue and reticulum is dependent more on the tempo of the degenerative changes and the age of the lesion than on any discernible difference in etiology. The uncertainty of classifying these cases into the two aforementioned categories is revealed by the disagreement in the interpretation by various authors. Cases, almost identical in structural changes, are regarded as inflammatory by some and as simple non-inflammatory by others.

I recently had the opportunity of studying two unusual cases of atrophy; one representing a fairly early, and the other a late, stage of the disease. They are given in detail, because they illustrate clearly the nature of the changes.

Case 1.—*History.*—A white woman, aged 27, called a physician on Oct. 23, 1929, because of headache, nausea and vomiting. She had a marked brownish pigmentation of the skin. On October 25, she complained of headache, drowsiness and insomnia. She was given morphine. On the morning of October 26, she had three spastic convulsions; the temperature rose to 100 F.; the pulse rate remained at from 75 to 80, but was weak. The urine was normal; the blood sugar was normal. The patient died on October 26.

Autopsy.—The body was well developed, slender, 163 cm. long, and weighed 100 pounds (45.4 Kg.). There was fairly marked cyanosis of the face. Definite brown pigmentation of the skin of the face, the anterior axillary folds, the nipples, the umbilicus and of the skin below the knees was present. The hands, forearms and face were especially dark. The subcutaneous fat was scant. The heart weighed 140 Gm. The valves were normal. The right coronary had three openings into the aorta. The heart muscle appeared brown. The root of the aorta was normal, except for two small vessels, one having its origin at the arch, between the innominate and the carotid arteries, and one between the carotid and the subclavian arteries. These vessels went to the neck. The lungs showed

moderate congestion at the bases. The spleen weighed 150 Gm. The follicles were prominent. Each kidney weighed 100 Gm.; the appearance of each was normal. Numerous small subperitoneal hemorrhages were present throughout the fallopian tubes. The mediastinal and mesenteric nodes varied in diameter to 1 cm. On section, they showed brownish pigmentation.

Both suprarenal glands were very small and thin; the maximum thickness was 3 mm. There was a small extravasation of blood in the tissues about these glands. The surfaces were fairly smooth and deep reddish brown. On section, the surface was extremely dark. The normal markings could be distinguished. There was no evidence of thrombosis of the vessels.

Anatomic Diagnosis.—The conditions were diagnosed as: primary contracted suprarenal glands, brown pigmentation of the skin, subperitoneal hemorrhage about the fallopian tubes and congenital anomaly of the aorta.

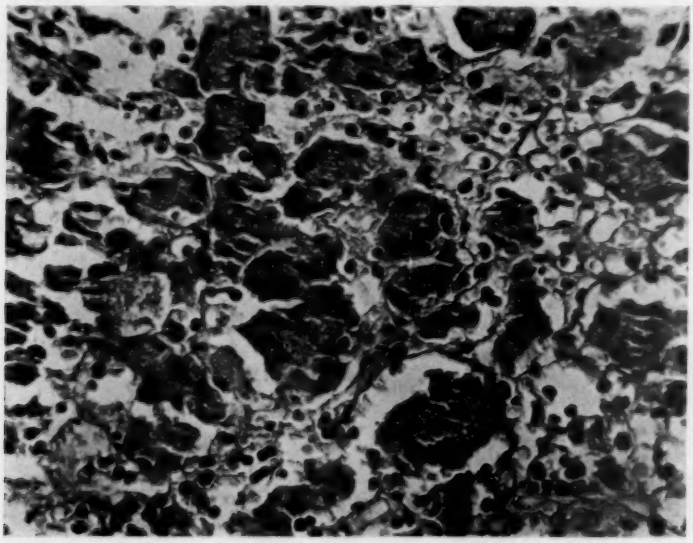

Fig. 5.—Early degenerative changes in cortical cells; slight retraction of cells from reticulum.

Microscopic Examination of the Suprarenal Glands.—Sections were stained with Harris' hematoxylin-eosin, Heidenhain's azocarmine, and the potassium ferrocyanide stain for hemosiderin. The histologic changes were as follows: The cortex was about one third of its normal thickness. The normal arrangement of the three layers was lacking. In places, columns of cells resembling the zona fasciculata were present, and, in places, small subcapsular clusters of cells resembling the zona glomerulosa. The medullary tissue was of normal thickness. Here and there in small areas the medullary tissue was replaced by dense clusters of lymphocytes. The cortex was the seat of marked changes. Figures 5, 6, 7 and 8 illustrate the changes seen throughout the gland. In figure 5, the cortical cells are seen in the process of contraction and withdrawal from the reticulum. The relation of the cells to the reticulum is brought out clearly by the azocarmine stain. The cells are decreased in number, their borders are poorly defined and, in places, clusters of these cells give the appearance of multi-

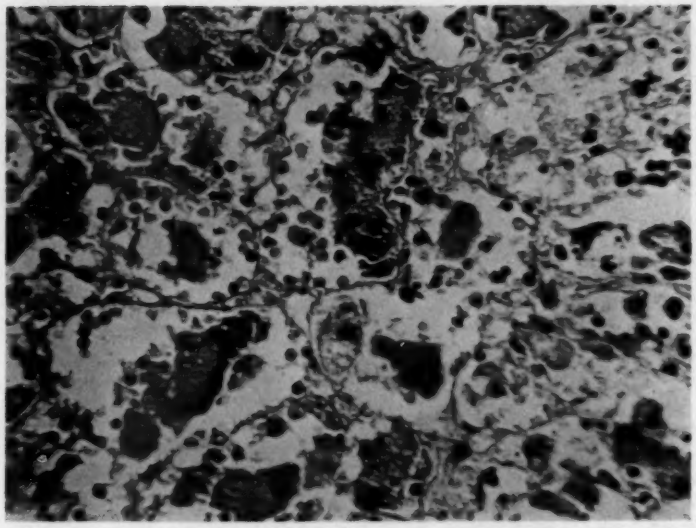

Fig. 6.—Further advanced stage: Cortical cells show marked degenerative changes. Reticulum is intact. Spaces formerly occupied by cortical cells contain red blood cells, cellular débris and lymphocytes.

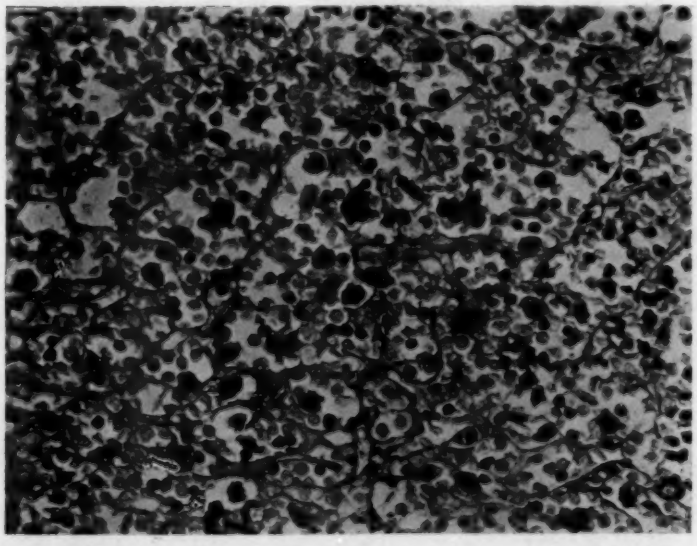

Fig. 7.—Far advanced stage: Few epithelial cells remain. The reticulum is partially collapsed.

nucleated giant cells. Their cytoplasm contains an occasional vacuole, but, for the most part, it stains more deeply and darker than the normal spongioblast. The nuclei vary in size and in staining qualities. Karyolysis and pyknosis are present. As a result of retraction of these cells, large spaces are present between the reticulum and the cells. In places, these are filled in by red blood cells; in other places, they are empty. Figure 6 shows a more advanced stage. Only a few cells are present, and these are in the process of disintegration. The reticulum is closer together, and the spaces left by the disintegrating cells are filled in by red blood cells, lymphocytes and plasma cells. In figure 7, the parenchyma is almost entirely absent, leaving only the partially collapsed network of reticulum. In other areas, the reticulum is completely collapsed and flattened out into fenestrated laminae, which lie parallel to the capsule. Throughout the cortex there is a diffuse infiltration of lymphocytes, plasma cells and an occasional

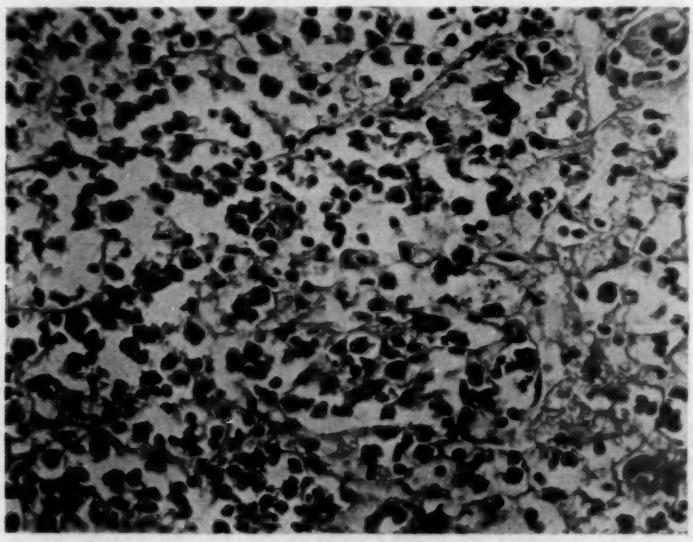

Fig. 8.—Area showing almost complete disappearance of cortical cells with marked infiltration by lymphocytes and plasma cells and extravasation of red blood cells.

macrophage containing hemosiderin. The infiltration is more abundant beneath the capsule. The capsule shows no evidence of thickening. The larger veins and arteries show no evidence of disease. A small amount of extravasation of blood is seen in the pericapsular region.

Case 2.—*History.*—A woman, aged 50, a housewife, had always enjoyed good health. She was the mother of four children. Eight years before this study she had an attack of influenza from which an uneventful recovery was made. An uneventful menopause occurred eighteen months before. Fifteen years before, she began to notice a darkening of the skin, first over the face and hands. This increased in severity until it became generalized. Four or five years previous to examination, the mucous membrane of the tongue and cheek became pigmented. She had been troubled since childhood with periodic attacks of diarrhea. Shortness of breath on exertion had been present for a few years. Until eighteen

months before, her strength was good, but this began to fail, and there had been a steady loss of strengh since that time. Weakness was very marked in the last few months before examination.

Examination.—Examination showed a high grade negroid pigmentation, particularly marked over the face, neck, hands, forearms, groin, vulva and areas subjected to pressure. There were blackish patches of pigmentation over the lips and brownish patches on the tongue and the buccal mucous membranes. The blood pressure was as follows: June, 1927, 140 systolic and 90 diastolic; Oct. 14, 1927, 130 systolic and 70 diastolic; Dec. 7, 1927, 104 systolic and 70 diastolic; April, 1928, 104 systolic and 70 diastolic; September, 1928, 90 systolic and 65 diastolic; Oct. 5, 1928, 96 systolic and 70 diastolic. Examination of the blood showed: hemoglobin, 56 per cent; red blood cells, 4,760,000; white blood cells, 6,000; lymphocytes, 36 per cent; eosinophils, 4 per cent; mononuclears, 22 per cent; polymorphonuclears, 38 per cent. The Wassermann reaction was negative. The van den Bergh test was negative for bilirubin. Blood urea was 10 mg.; creatinine, 1 mg., and blood sugar, 0.084 per cent. The basal metabolic rate was minus 3 per cent. There was absence of free hydrochloric acid; the total acidity was estimated as 10 degrees.

Course.—In the last few months, the patient rapidly lost strength and weight and died of progressive exhaustion on Oct. 12, 1928.

Autopsy.—The body was fairly well developed, but poorly nourished. There was marked pigmentation of the entire body, the color resembling that of a dark mulatto. The neck, face, backs of the hands and forearms were especially pigmented. The creases of the palms, neck and axillary folds were very dark in color; an accentuation of pigmentation was noted about the hips, knees and lateral portions of the feet. The mucous membranes were involved, as noted. The skin was smooth and thin, with no desquamation. The subcutaneous fat was scant. The thymus measurements were 60 by 30 by 25 mm.; the weight was 16 Gm. The thymus was firm and light reddish brown. The heart weighed 180 Gm.; it showed brown atrophy. The lumen of the aorta was 1.7 cm. in diameter at the proximal portion of the arch. There was slight hypostatic congestion at the base of each lung. The spleen weighed 175 Gm.; the markings were normal. The liver was small. The stomach showed no lesions. The pancreas showed nothing of note.

The right suprarenal gland was found after considerable search; its dimensions were 30 by 20 by 2 mm. The cortex appeared as a narrow zone composed of a glistening, grayish-white tissue. The center was grayish brown. Although prolonged search was made for the left suprarenal gland, it was not found. There was no evidence of accessory interrenal or chromaffin tissue. The kidney showed the horseshoe type of deformity. The lymph nodes about the aorta and in the mesentery varied in size from a few millimeters to 1.5 cm. in diameter. The thyroid gland was of normal size and appearance.

Anatomic Diagnosis.—The conditions were diagnosed as: primary contracted suprarenal gland (right), aplasia (?) of the suprarenal gland, pigmentation of the skin, horseshoe kidney, brown atrophy of the heart, hypostatic congestion of the lung and emaciation.

Microscopic Examination.—A dark granular pigment was present in the rete malpighii of the skin. The thymus contained a broad medulla and was rich in Hassall's corpuscles. Solitary follicles in the intestines appeared large. Their secondary follicles were very active and were surrounded by a broad zone of lymphocytes. The semilunar ganglions appeared normal. The lymph nodes showed

a marked activity of the secondary follicles. The sinuses were loaded with phagocytes. The thyroid gland contained large numbers of lymphoid follicles, some of which showed germinal centers; these were situated between the lobules and, in places, within them. The acini were poor in colloid. Degenerative changes were present in the epithelial cells.

Microscopic sections were taken through many parts of the right suprarenal gland and stained with Harris' hematoxylin-eosin, Pappenheim's pyronin-methylene green, van Gieson's stain and Heidenhain's azocarmine and by Mallory's method for demonstrating hemosiderin.

The cortex was almost entirely lacking; it was reduced to a thin streak of hyalinized connective tissue, poor in nuclei. A few plasma cells and lymphocytes were scattered throughout the capsule. Directly beneath the capsule there were, here and there, dense collections of lymphocytes, plasma cells and phagocytes containing hemosiderin granules. The capsule appeared slightly thickened. In places there were small clusters of cortical cells that occupied the entire thickness of the gland. Some of these cortical masses appeared encapsulated. The cells varied considerably in size and were atypical in arrangement. The nuclei showed marked variation in size and staining qualities. Their cytoplasm was homogeneous, pink-staining and poor in fat. Small engorged capillaries ramified between these cells. In places, these nodules were infiltrated by lymphocytes and plasma cells and often showed marked degenerative changes. About these nodules, the collection of round cells was very dense. The center of the gland was occupied by clumps of fairly deep-staining cells which had round to oval nuclei. Some of these cells were connected to each other by protoplasmic processes. Large dilated sinuses and capillaries were in close contact with them. In places, they closely simulated the structure of the medulla, but in other portions it was impossible to state definitely whether these were cortical cells or medullary cells. (Chromaffin stains were ineffective, as the tissues were not obtained until more than twenty-four hours after death.) In places, accumulations of round cells embedded in a loose reticulum replaced almost the entire thickness of the gland.

Figure 9 shows a section of the suprarenal gland in which there was an absolute increase of connective tissue, which was fairly vascular and replaced the parenchyma. It was sharply delimited from the normal tissue, which resembled the medulla in structure. The majority of sections, however, showed no actual increase of connective tissue; the increase was only relative and was due to the collapse of the reticulum. Figure 10 illustrates a cross-section of the gland, in which there was little or no evidence of connective tissue reaction (compare with fig. 9). The veins showed no evidence of thrombosis. About some of the smaller veins were dense accumulations of plasma cells, phagocytes and lymphocytes. The pericapsular region contained a small amount of extravasated red blood cells.

Case 1 illustrates very clearly the stages in the disappearance of the cells of the cortex. The inflammatory reaction was secondary to the degenerative changes and consisted for the most part of lymphocytes and plasma cells. The reticulum was not destroyed, but collapsed following the disappearance of the cortical cells. The place left by the cortical cells was partially filled by red blood cells, a condition that is very similar to that seen in red atrophy of the liver.

Case 2 shows a much further advanced stage of the disease. Little cortical tissue remained and only a thin zone of collapsed reticulum

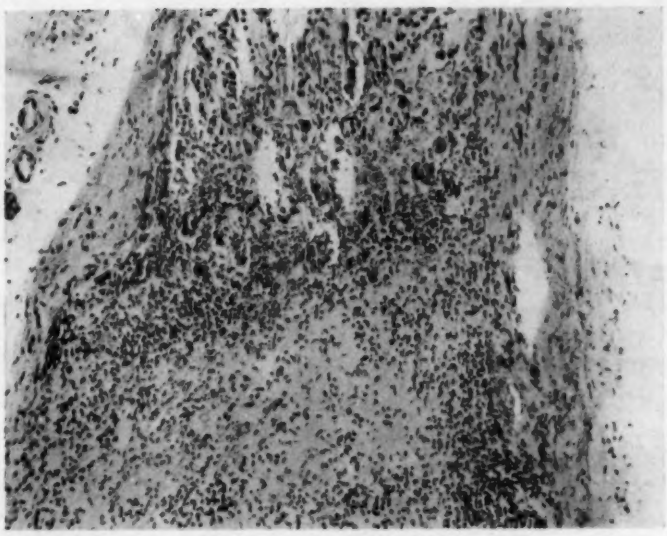

Fig. 9.—Cross-section through gland showing fibrosis of entire thickness. Adjacent to this is normal medullary tissue. Cortical tissue is absent.

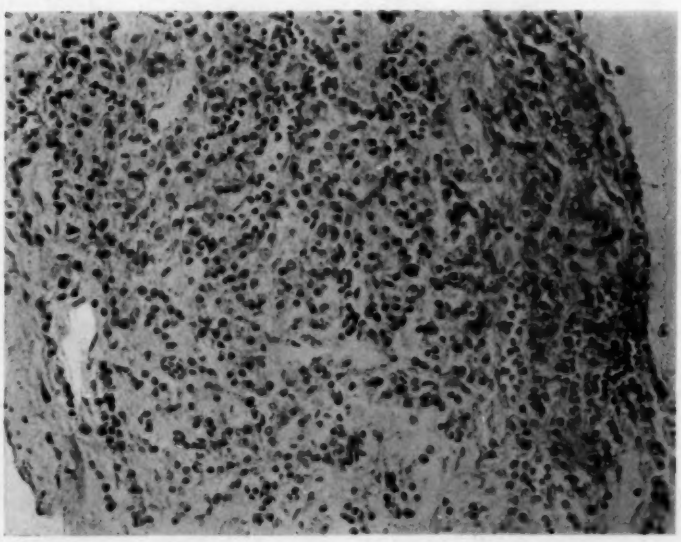

Fig. 10.—Cross-section through entire thickness of gland, showing medulla of normal thickness. Cortex is absent. There is no inflammatory reaction.

marked the remains of the cortex. The medulla was secondarily involved by the inflammatory reaction in the cortex, but a large part of it was preserved. Small nodules resembling hyperplastic cortical adenomas were present. These adenoma-like nodules also showed degenerative changes.

Structural Changes in the Cases Reported in the Literature.—The glands are markedly reduced in size. Their weight varies from 0.75 Gm. to 3 Gm. They are very thin, often of the thickness of paper. One gland may be smaller than the other, but the difference in weight is not great. Aplasia of one gland and atrophy of the other are described in two cases (Arnett, Hempelmann). The color varies from gray to brownish-red. In most cases, the surfaces are flat and smooth; nodular elevations are prominent in the cases described by Kiefer, Scott, Held, Lucksch, Kovacs and Matras. The resemblance to the surface of a cirrhotic liver is often striking. Adhesions to the surrounding structures are reported in only one case (Rössle).

On section, the medulla and the cortex are not readily defined. The latter may appear as a gray streak, forming a great part of the thickness of the gland. Small, well circumscribed nodules, varying in color from yellow to brownish-red, may obscure the markings. The thickened capsule may appear as a thin, grayish-white membrane. Even in extreme cases the trilobed shape of the organ may be retained.

Microscopically, the lesions in most cases are limited to the cortex, and the involvement of the medulla appears to be secondary. The extent of the involvement of each layer, as far as can be determined, is as follows: the cortex partially or completely destroyed and the medulla normal or slightly involved, thirty-three cases; the cortex and the medulla equally diseased, seven cases; the medulla and the cortex both diseased, the medulla more than the cortex, five cases.

The microscopic changes in the cortex are variable. Little of the normal stratified layer remains, and the cortex is markedly reduced in thickness. The cortical tissue in places is completely absent, so that the medulla, when present, lies adjacent to the capsule. Occasional remnants of the zona glomerulosa and of the zona fasciculata are present. In places, only the loose reticular stroma remains, containing dilated and engorged capillaries. Kraus and Hübschmann liken this to red atrophy of the liver. Remnants of cortical cells may be embedded in a dense infiltration of lymphocytes and plasma cells. Degenerative changes in cortical cells are almost constant. They are most pronounced in the cases described by Held, Medlar, Kiefer and Lucksch. They consist principally in loss of cellular outline, swelling of cells, vacuolar and fatty degeneration, loss of lipoid, nuclear degeneration and fusion of cells to form large multinucleated forms.

Regenerative changes in the cortical cells are present principally in two forms, namely: in scattered islands of cells and in large, well circumscribed, adenoma-like nodules. This is more marked in some cases than in others. In the cases of Kraus, Bittorf, Bloch and others, there is little or no evidence of regeneration. Adenoma-like nodules are particularly prominent in the case reported by Kiefer and to a lesser degree in those of Lucksch, Kovacs, Held, Hübschmann, Rössle, Fahr and Reiche. These consist of small areas of cortical cells encapsulated by connective tissue. The cells resemble the zona fasciculata and at times the zona glomerulosa. The nuclei show considerable variation in size, shape and chromatin content. An occasional mitosis was observed by Kovacs. The cytoplasm is poor in lipoids. Degenerative changes are common in the center, and not infrequently the entire nodule is degenerated. Infiltration of these nodules by lymphocytes may be marked. At times, connective tissue and often a dense cellular infiltration replaces, in part, the area in which the cortical cells have disappeared. The cells consist mainly of small lymphoid-like cells, plasma cells and large macrophages, the latter often containing granules of hemosiderin. In a number of cases (Bloch, Schmidt, Wahl, Lucksch, Kovacs, etc.) there is little or no connective tissue replacement of the cortex. Frequently, there is a diffuse infiltration of small lymphoid cells in a loose reticulum immediately beneath, and often penetrating, the capsule. Bloch believed that these are sympathetic-formative cells. Held, Hübschmann, Furuta, Kovacs and others regarded these as inflammatory. Paunz expressed the belief that they arise from the reticulo-endothelial cells in response to irritation. Large accumulations of lymphocytes may occupy the entire thickness of the glands. Small areas of extravasation of erythrocytes are often present. In the cases reported by Rössle and in cases 1, 2 and 3 reported by Fahr and Reiche, the inflammatory changes are more conspicuous than in the cases reported by others. Rössle's case showed hemorrhagic areas of necrosis in the cortex. Fahr and Reiche described a perivenous infiltration of granulation tissue. Perivascular round cell infiltration was mentioned by Kovacs and Kraus. A sharp demarcation between cortex and medulla is often lacking. Hübschmann found it difficult to distinguish the surviving medullary from the cortical tissue.

The medulla occasionally shows a reduction in size, infiltration by lymphoid cells and, rarely, connective tissue replacement. Bloch traced transition stages from the small sympathetic-formative cells to chromaffin cells. This was also mentioned by Wahl and Lucksch. Complete destruction of medulla was mentioned by Wakefield and Smith. The chromaffin reaction is variable.

Changes in the pericapsular tissue are slight. Small groups of lymphoid cells are occasionally present. Small cortical rests in the capsule are described. Vascular changes are absent. The nerves and sympathetic ganglion cells are not altered.

Etiology.—In 1903, Simmonds [167] found two cases showing perivascular infiltration and endarteritic proliferation which suggested syphilis as a causative factor. In the majority of his cases, however, these changes were lacking. Later, Simmonds [498] found in early congenital syphilis inflammatory thickening of the capsule and secondary involvement of the cortex. He suggested that this change may lead to the disappearance of the cortex, but he was not able to demonstrate the process in older persons. He finally concluded that though syphilis must be considered, it cannot be proved to be an etiologic factor. Recently Fahr and Reiche described a perivascular infiltration of lymphocytes and granulation tissue, suggesting a syphilitic infection, in three cases. In only one case, however, was there a history of syphilis, and in every instance anatomic evidence of syphilis elsewhere was absent. Hübschmann's cases did not show vascular alterations, but showed lesions in the liver suggestive of syphilis. A history of syphilis of two years' duration was obtained in the case described by Fiessinger and Leroy. In the remaining cases, there is no evidence of syphilis. There is little proof, therefore, that syphilis is a causative factor, except in rare instances.

Still less proof is available that the lesion is tuberculous. Granulomatous lesions, tubercles, caseation, calcification and adhesions to the surrounding tissues are lacking. In tuberculosis of the suprarenal glands, it has been shown that the medulla is involved earlier than the cortex, and that the lesions are more extensive in the former than in the latter. The majority of cases of primary contracted suprarenal gland show little or no change in the medulla.

A congenital hypoplasia or disturbance in the development of the glands is considered by Neusser, Wiesel, Bloch and Wahl. In a detailed histologic study, Bloch found transitional stages in the development of chromaffin cells from small round cells which he regarded as embryonic sympathetic-formative cells. He considered that this was an effort at compensatory hyperplasia of the medulla which was retarded in development. Paunz opposed the belief that these are sympathetic-formative cells, believing that they are histiocytes in the sense of Aschoff, which are derived from the reticulo-endothelial system. Oberndorfer considered that the cells in the medulla, interpreted by Wiesel as sympathetic-formative cells, are merely collections of lymphocytes and plasma cells, and quoted Aschoff, who also failed to confirm Wiesel. Bloch's theory failed to account for the marked degenerative changes in

the cortical cells, which appear to be the primary site of the disease, the medullary changes being secondary. It is also difficult to conceive of congenital hypoplasia, or underdevelopment, of the suprarenal gland in which no symptoms are present until as late as the fifth or sixth decade.

The susceptibility of the suprarenal glands to acute and chronic diseases elsewhere in the body has been strongly emphasized in recent years. Dietrich and Siegmund found degenerative changes in the cortical cells with round cell areas in chronic septic marasmus, and suggested that these changes may lead to replacement by scar tissue and atrophy of the organ with symptoms of Addison's disease. Thomas found marked vacuolar degenerative changes in the cortex in diphtheria, and marked edema and granular degeneration in scarlet fever. Degenerative changes in the course of infectious diseases were described by Weisenfeld, Wülfung, Goldzieher, Oberndorfer and others. More recently, Paunz made a study of histologic changes in the 1,171 suprarenal glands under various conditions. He found changes in 197, or 17 per cent. These changes consisted principally in the formation of plasma cells, lymphocytes and macrophages from the reticulum, and he distinguished three groups according to the distribution and type of reaction. In 7 cases, he found marked connective tissue replacement of the cortex. The majority of cases occurred in the third decade and were associated with the following conditions: acute inflammation, 20 cases; simple chronic inflammation, 27 cases; chronic caseous tuberculosis, 8 cases; syphilis, 16 cases; lymphogranulomas, 2 cases; tumors, 52 cases. Bernard and Bigart investigated the suprarenal glands in 30 cases of tuberculosis and found perivascular sclerosis of the zona fasciculata with secondary changes in the parenchyma. In several cases, marked atrophy of the parenchyma with sclerosis resulted. Kioyokawa, in a more extensive study, found sclerotic changes in the suprarenal glands in 20 of 100 cases associated with tuberculosis elsewhere in the body. These changes consisted of an increase of connective tissue about the capillaries in the zona fasciculata and degenerative changes in the parenchyma. He designated this condition as tuberculotoxic suprarenal cirrhosis

From this brief review it is evident that in a number of acute and chronic diseases the suprarenal gland may be the site of marked degenerative changes. The changes are not peculiar to any disease and are not constant. They are not comparable to the changes seen in primary contracted suprarenal gland.

Perivascular sclerosis, which is constant in the "tuberculotoxic cirrhosis" of the suprarenal gland is not present in primary contracted suprarenal gland. A marked diminution in size of the organ is striking in primary contracted suprarenal gland, whereas it is rarely seen in the

changes associated with an infectious disease. As suggested by Kovacs, the changes described by Dietrich and Siegmund in infectious diseases and chronic marasmus are analogous to fatty degeneration of the liver, whereas in primary contracted suprarenal gland, the changes are similar to cirrhosis of the liver. A history of long standing infection is lacking in the reported cases of primary contracted suprarenal gland. In sixty-eight cases of primary contracted suprarenal gland, the past illness as recorded in the histories are as follows: rheumatic fever, three cases (four years, eighteen years and twenty years, respectively, preceding the onset of symptoms of Addison's disease); empyema, one case; pulmonary tuberculosis, one case; influenza, two cases; bronchitis and asthma, one case; typhus, one case (thirty years preceding the onset); suppurative angina, one case (three and one-half years previous to the onset); typhoid fever, one case (eleven years previous to the onset); malaria, one case, and syphilis, two positive cases and one questionable case.

It is improbable that the incidence of chronic infections is greater in primary contracted suprarenal gland than in any other chronic disease.

In summary, it may be stated that the etiology of primary contracted suprarenal gland (atrophy) is still unknown. The pathologic changes indicate that the condition is primarily a slow degeneration involving the cortex and leading finally to the disappearance of the cortical cells. The inflammatory reaction is variable and may be regarded as secondary, the degree of it depending on the severity and tempo of the degenerative changes. Partial function is maintained by regeneration in the form of small adenoma-like islands of cortical cells. These later may also undergo degenerative changes. There is little evidence that these changes are due to infectious processes in the suprarenal gland. The changes may well be likened to subacute atrophy of the liver. Kovacs, and recently Omelskyj, suggested that the changes are due to a circulating toxin of unknown nature which has a specific action on the cortical cells. They accordingly designated the condition "cytotoxic contracted suprarenal gland." There is as yet little evidence in support of this theory.

AMYLOIDOSIS OF THE SUPRARENAL GLAND

Amyloidosis of the suprarenal gland until recent years has not been considered a cause of Addison's disease. Similar to metastatic carcinoma, amyloid deposits in the suprarenal gland are a common occurrence, but the injury to the parenchyma in most cases is not sufficiently extensive to give rise to symptoms of Addison's disease. Six cases of Addison's disease associated with amyloidosis of the suprarenal glands are included in the literature (Bittorf, Schlesinger, Schultz, McCutcheon, Hunter and Rush and Philpott). A case reported by Bauer is doubtful. The associated lesions are: pulmonary tuberculosis, three cases; tertiary

syphilis, one case; hypernephroma, one case; tuberculosis and syphilis combined, one case. Amyloid deposits in other viscera are usually present. In McCutcheon's case, the sympathetic ganglions, thyroid gland, hypophysis and pancreas were similarly involved.

Macroscopically, the organs appear normal or slightly increased in size, are firm and vary in color from gray to yellow. On section, the two layers are readily distinguishable. The deposits are principally in the zona fasciculata and zona reticularis. Amyloid is present outside of the endothelium of the capillaries and between the cortical cells, resulting in marked atrophy of the parenchyma and partial closure of the lumina of the vessels. The medulla may show a slight diminution in size and small deposits of amyloid, particularly about the small vessels. Clinically, the diagnosis is often difficult because of the symptoms of the underlying condition.

FATTY DEGENERATION

Fatty degeneration was reported in three cases. Loeper and Ollivier described a case of fatty degeneration of both suprarenal glands in a woman, aged 30, who had typical clinical manifestations of Addison's disease. In Schnyder's case, the clinical picture is not convincing. One organ is missing, whereas the opposite organ shows hypertrophy and fatty degeneration of the cortex. The cause of these changes is not understood.

TUMORS

Primary tumors causing symptoms of Addison's disease are noted in three reports. Riemer reported a case of paraganglioma in a woman, aged 46. Hertz and Secher noted pigmentation of the skin in a youth, 16 years of age, who showed a neuroblastoma of the suprarenal glands, with metastases to other organs. An endothelioma of the suprarenal glands accompanied by all the cardinal symptoms of Addison's disease was reported by Black. Metastatic tumors rarely cause Addison's disease, as judged by the recent case reports. Bilateral metastatic tumors are frequent and often extensive, but rarely give rise to symptoms of Addison's disease. Little suprarenal tissue is recognizable grossly, but microscopically one finds abundant nests of surviving parenchyma. The incomplete destruction of the suprarenal glands in metastatic carcinoma may account for the absence of symptoms of Addison's disease.

VASCULAR LESIONS

Bilateral massive hemorrhage into the suprarenal glands is not infrequent in adults, following acute septic conditions. Death is usually rapid and often accompanied by symptoms simulating peritonitis. Unilateral thrombosis of the suprarenal vein is not infrequently encoun-

tered, but is usually symptomless. Bilateral thrombosis of the suprarenal veins associated with Addison's disease was reported by Straub, Veit and Kovacs. In Straub's case, symptoms of pigmentation and weakness developed in seventeen days following thrombosis. Veit reported a case in a widow, aged 50, in whom symptoms appeared in the course of from four to five weeks. In Kovacs' case, the lesion is of longer duration, the symptoms, however, being manifested only a few days before death.

In the early stage, the organ is usually enlarged and dark in color. The medulla is first involved and later the cortex. The central part is replaced by a dark red, firm tissue. In the later stages (Kovacs), the organ is shrunken, the capsule is thickened, and there is partial organization of a central detritus which contains abundant cholesterol and blood pigment.

Anemic infarction was present in a case described by Furuta. Destructive cortical lesions resulting from multiple arteriolar emboli in the course of an ulcerative endocarditis was seen on microscopic study. Macroscopically, the organ appeared normal.

MISCELLANEOUS LESIONS

Aplasia of one gland is rare. When associated with Addison's disease, the opposite organ is usually the site of pronounced anatomic changes. In agenesis of one suprarenal gland, the right without exception is the side involved (Hecht, Miloslavich). There is usually an associated developmental anomaly of the kidney of the same side or of the genital organs (Miloslavich).

There are six case reports of aplasia of one suprarenal gland associated with Addison's disease. The right side was involved in four cases and the left in two. Four of these cases were associated with atrophy of the opposite organ. In one case, the opposite organ showed hypertrophy and venous thrombosis (Veit). In another case (Schnyder), the opposite organ was hypertrophied and showed fatty changes. The clinical picture in this case was not convincing.

Addison's disease following trauma was reported by Bormann and Dürck. Bormann's case showed hyperplastic chronic inflammatory changes with degeneration of the parenchyma which was attributed to trauma. In Dürck's case, symptoms followed fracture of ribs. Symptoms of varying intensity were present for seven and a half years. The suprarenal glands were small and were replaced by scar tissue. The presence of blood pigment in the suprarenal glands suggested hemorrhage and thrombosis of traumatic origin. Clinical cases of Addison's disease following trauma are reported by Riemer and Lescheziner. Abscess formation due to pneumococcus following pneumonia was

described by Roth. Fritz described a case in which there occurred bone marrow metaplasia of the suprarenal gland.

ADDISON'S DISEASE WITHOUT LESIONS IN THE SUPRARENAL GLANDS

Four cases of Addison's disease without lesions in the suprarenal glands were reported. Briefly these were as follows:

CASE 1 (Richon).—A girl, aged 10, had always shown a brownish tint of skin. The father died of tuberculosis. The paternal grandfather and aunt had a remarkable coloration of the skin. The father and the mother were not dark. During the two months before examination, the patient's skin had become darker. The mucous membrane of the mouth was pale. For two months, there had been weakness and inability to attend classes. Early physical signs of apical tuberculosis were present. No gastro-intestinal symptoms were noted. The patient was given subcutaneous injection of extract of suprarenal capsule. On the fifth day, there were vomiting and an increase of weakness. The patient improved and was discharged from the hospital on the twentieth day. Three and one-half months later, pigmentation of the skin was almost gone. The patient's strength and general condition improved. Eleven months later, she was readmitted, with vomiting, abdominal pain, diarrhea, a return of pigmentation of the skin, loss of weight and a yellowish color of the soft palate. She was given epinephrine by mouth. The coloration of the skin deepened. About one month later she died.

Postmortem examination revealed: tuberculous infiltration of both upper lobes; fibrinous pleuritis; cretaceous change in the bronchial nodes; tuberculous ulceration of the lower ileum, with perforation 5 cm. from the ileocecal valve; 200 cc. of fluid in the peritoneal cavity; normal sympathetic ganglions of the celiac plexus except for an increase of connective tissue, and an absence of change, either gross or microscopic, in the suprarenal glands.

CASE 2 (Nobécourt and Brelet).—A boy, 1¼ years old, showed slight pigmentation of the skin. The mother had pulmonary tuberculosis. The patient's pigmentation seemed to increase while he was under observation. There was no pigmentation of the mucous membranes. The patient showed marked asthenia, loss of weight, constipation and bronchitis. The asthenia became more pronounced, and the patient died three weeks after admission.

Postmortem examination showed: marked miliary tuberculosis of the lungs of recent origin; caseous mediastinal and mesenteric nodes; tuberculous meningitis, and no change, gross or microscopic, in the suprarenal glands.

CASE 3 (Sbrozzi).—A woman, aged 26, previous to admission had suffered from pain and swelling of the joints accompanied by a high temperature. On therapy, the pain and swelling of the joints disappeared, but the high temperature continued. Vomiting and diarrhea became marked. There was a diffuse bronchial catarrh, with a systolic murmur over the pulmonary area. Extrasystole was noted. The spleen was enlarged. A few days after the patient's admission bronchopneumonia developed. The color of the skin turned dark, especially in the folds of the body and in the inguinal region. Profuse diarrhea developed, and the patient died.

Postmortem examination showed: red hepatization of the right lower lobe; bronchopneumonia of the left lower lobe; fibrinous pleuritis; verrucous endocar-

ditis; acute splenic tumor, and no gross or microscopic alteration of the cortex or of the medulla of the suprarenal glands.

Case 4 (Debove).—A man, aged 41, had chronic alcoholism, with symptoms of cirrhosis of the liver, for which he had been treated on a previous admission to the hospital. Erysipelas of the face developed, and he reentered the hospital. The erysipelas responded readily to treatment. Following this, the patient showed the development of pigmentation of the skin. He claimed that he had always been brown. The color was that of a mulatto. Pigmentation was more marked in the groin and axilla. Anorexia, pronounced diarrhea, vomiting and loss of weight developed. The blood pressure was 90 mm. of mercury. Marked weakness was shown.

Postmortem examination showed: ascites; the ascitic fluid contained tubercle bacilli. The liver weighed 780 Gm., and showed typical atrophic cirrhosis. The left suprarenal gland weighed 22 Gm.; the right, 7 Gm. There was a mild degree of sclerosis of the capsules of the suprarenal glands. On microcopic examination, all layers were intact; there was no evidence of tuberculosis. There was an area of fibrosis about the celiac axis, which extended laterally over both suprarenal glands.

In case 1, the patient had been dark since birth; an increase in pigmentation had been noted shortly before admission. The mucous membranes were not involved. A deepening of the color of the skin is sometimes seen in cases of advanced tuberculosis. It is also probable that in this case the severe tuberculosis of the lungs accounted for the asthenia and the gastro-intestinal symptoms. The same objections may be raised in case 2. In case 3, the major symptoms were those of verrucose endocarditis. The pigmentation was not typical, as the mucous membranes were not involved. Since the gastro-intestinal symptoms and adynamia followed the development of the terminal pneumonia, they may be regarded as a manifestation of toxemia. In case 4, it is probably that the far advanced cirrhosis of the liver was responsible for some of the symptoms interpreted as those of Addison's disease. Here, again, pigmentation of the mucous membranes was lacking. The blood pressure was only moderately reduced, and the weakness and the gastro-intestinal symptoms were terminal.

These cases, therefore, cannot be considered as important evidence for the theory that Addison's disease can occur without changes in the suprarenal glands.

CHANGES IN OTHER ORGANS

THYMUS AND LYMPH NODES

The weight of the thymus is given in twenty-nine cases of Addison's disease. These are plotted in figure 11 on a thymus weight curve of normal persons who met with accidental death. The normal curve was obtained from Hammar's tables.

The mean weight of the thymus of normal persons is designated by the continuous line; the second and fourth quartiles, by the coarse

broken line, and the maximum and minimum, by the dotted lines. The weight of the thymus in normal persons increases rapidly until the fifteenth year, after which there is a fairly steady but slow decline in weight. The normal variation in the weight of the thymus is very great; the interval between the mean and the maximum even in well advanced life varies from a few grams to 45 Gm.

The cases of Addison's disease in which weights of the thymus are given are divided into three groups, viz.: (1) cases in which there had been no loss of body weight preceding death; (2) cases in which the state of nutrition cannot be determined from the case reports, and (3) cases in which there had been loss of body weight preceding death. Only one case (Rössle) lies above the maximum, but this case is com-

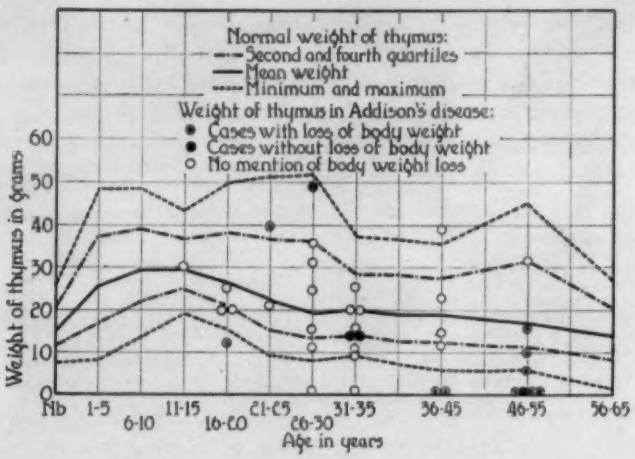

Fig. 11.—Weight of thymus in Addison's disease.

plicated by Graves' disease, which is frequently associated with enlargement of the thymus. Five cases lie close to the mean. Fifteen cases lie below the mean. In the remaining eight cases, no evidence of the thymus was found. These are given on the base line in figure 11.

Judging from the weight of the thymus alone, one readily sees that in Addison's disease the weight of the thymus does not exceed that found in normal persons who have died of accidental causes. It is probably higher than in cases of death from infectious diseases, and higher than in cases in which there has been a slow and gradual loss of weight. It does not reach the large dimensions found in Graves' disease or in myasthenia gravis.

However, to judge from the weight of the gland alone is misleading as this does not give any information as to the relative proportions of fatty tissue and parenchyma. This relation cannot be determined from

the cases at hand, as only few reports of the microscopic appearance of the thymus are given. In two cases reported by Hammar, there is an increase in the number of Hassall's corpuscles of the type iii, which he attributed to a toxic factor. The weight of the glands, however, was within normal limits. A few cases were reported in which the thymus contained a broad medulla or in which the appearance of the thymus in childhood was simulated.

Lymphatic hyperplasia was more frequently reported than enlargement of the thymus. Table 8 gives the frequency of lymphatic enlargement in tuberculosis of the suprarenal glands and in primary contracted suprarenal glands.

The condition of the lymph nodes is mentioned in the reports on sixty-four cases of tuberculosis of the suprarenal glands. In twenty-one cases, enlargement of all nodes was noted. In the reports of nine-

TABLE 8.—*Frequency of Lymphatic Enlargement in Tuberculous, and in Primary Contracted, Suprarenal Glands*

	Tuberculous Suprarenal Glands		Primary Contracted Suprarenal Glands	
	Number	Per Cent	Number	Per Cent
Generalized enlargement	21	32.81	10	21.28
Localized enlargement				
Follicles at base of tongue and tonsils	6	9.39	5	10.64
Peyer's patches	6	9.39	7	14.89
Mesenteric nodes	5	7.80	5	10.64
Retroperitoneal nodes	5	7.80	5	10.64
Other nodes	2	3.13	6	12.76
No enlargement	19	29.69	9	19.15
Total	64	100.00	47	100.00

teen cases, it is stated that the lymph nodes were not enlarged. In reports on primary contracted suprarenal glands, the condition of the nodes is given in a larger percentage of the cases. The distribution and frequency of enlarged nodes are somewhat similar to those observed in tuberculosis of the suprarenal glands.

As in thymic hyperplasia, the question is raised as to whether or not these enlargements are normal variations. I recently collected material for a study of the structure of normal lymph nodes in various parts of the body. The material was obtained from normal persons who had met with accidental death. It was found that, as in the case of the thymus, there is a wide variation in the size of the nodes in adults, as well as in children. Exact standards for comparison, however, are not available, and for the present the final answer to this question must be left open.

Wiesel,[517] Neusser and Wiesel, Hedinger and others designated these cases as status lymphaticus. They expressed the belief that in this

condition the chromaffin tissue is hypoplastic in the suprarenal glands and other parts of the body.

There are several objections to this theory. As has been shown, the evidence is not conclusive that the hyperplasia of the lymphatic tissue can be considered abnormal. In many cases of primary contracted suprarenal gland in which the lymphatic tissue is reported hyperplastic, the medullary tissue of the gland is not altered in quantity, the cortex being the main seat of involvement. In addition, there is little support for the theory that the extrasuprarenal chromaffin tissue, which normally undergoes involution, has any physiologic importance.

There is experimental evidence that the destruction of the adrenal glands in animals is followed by a hyperplasia of the lymphatic apparatus. The experiments of Marine, Manley and Baumann in rabbits, and of Jaffe in rats indicate that suprarenalectomy not only prevents involution of the thymus, but produces regeneration of a highly involuted thymus. Zwemer found that removal of the suprarenal glands in cats results in a hyperplasia of lymph nodes and enlargement of the spleen and thymus. Kahn, Rössle, Medlar and others held that there is a hyperplasia of the lymphatic apparatus in Addison's disease, but that this develops subsequent to the destruction of the suprarenal glands.

ENDOCRINE ORGANS

In Addison's disease it is uncommon to find symptoms referable to any of the glands of internal secretion, aside from the suprarenal glands. In seven cases symptoms of exophthalmic goiter were reported. These are the cases of Rössle, Courmont, Lesieur and Thévenot, and Head; one case from the records of the St. Thomas Hospital, London, and the cases of Löffler, Donath and Lampl, Étienne and Richard. Held's case showed symptoms of polyglandular involvement. The cases reported by Bendix presented symptoms of intermittent polyuria. Diabetes mellitus was present in the case reported by Arnett. Allan, Bonner and Calloway each report a case of cessation of menses at the onset of the disease. In most cases, however, there is little or no disturbance of menstruation. Impotence in man is not infrequently reported.

Pathologic changes in endocrine organs other than the suprarenal glands are frequently reported. The thyroid gland is most frequently involved. In association with primary contracted suprarenal gland, degenerative changes in the epithelial cells of the thyroid gland, lymphocytic infiltration and foci of lymphocytes containing secondary follicles in the intralobular spaces and not infrequently replacing the parenchyma are reported by Schmidt, Zondek, Bloch, Brenner, Kiefer and others. Dubois reported three such cases in association with tuberculosis of the

suprarenal glands. Hyperplasia of the thyroid gland was reported by Rössle and a colloid goiter by Löffler. Involvement of the pancreas was rarely described. Chronic interstitial pancreatitis was reported by Phillips and Arnett. Skirving and Welsh described hemorrhage into the pancreas, a rare occurrence in Addison's disease, whereas in experimental acute adrenal insufficiency in dogs, it is commonly seen (Stewart [502]). The ovaries and testes rarely show changes. Kraus reported degenerative changes in the hypophysis in almost all of his cases of Addison's disease. Polyglandular involvement was occasionally reported (Donath and Lampl, one case; Kreibig, one case; Wakefield and Smith, one case; Lucksch, one case; Kraus, two cases; Brenner, one case, and Held, one case).

The changes in other glands of internal secretion are inconstant and seldom of sufficient extent to give rise to symptoms of insufficiency. It is improbable that the changes are the result of a disturbance in the interrelationship of the glands, but, as suggested by Held and Schmidt, the changes are more likely the result of the action of some unknown toxic substance on the suprarenal gland and other glands of internal secretion.

GASTRO-INTESTINAL TRACT

In animals, following adrenalectomy, the presence of gastric and duodenal ulcers has been frequently observed. Mann found that following the removal of both adrenal glands in sixty dogs and five cats gastric lesions developed in forty cases. These consisted of hemorrhages, erosions and well formed ulcers. In five cases, duodenal ulcers were also present. In animals dying shortly after operation, ulcers did not occur; they occurred only in animals that lived one or more days. These results were also obtained by Elliott and Finzi, working independently. Jaffe reported the frequent occurrence of hemorrhagic erosions of the gastric mucosa following bilateral adrenalectomy. Stewart,[502] in his recent review of experimental work on adrenalectomized dogs, stressed the marked gastro-intestinal disturbance that ushers in the terminal stage of the disease. In most of these animals, the gastro-intestinal tract shows a marked hemorrhagic congestion. Stewart suggested the hypothesis that some toxic substance that develops following adrenalectomy is eliminated through the gastro-intestinal tract. He also suggested that this congestion may be due to deficiency of the regulatory hormone that is normally secreted by the suprarenal glands.

In the cases collected from the literature changes were noted in the gastro-intestinal tract, as set forth in table 9. The gastro-intestinal tract is definitely reported to be without changes in only twenty-one

cases, but it is probable that a much larger number showed no change, since in many cases absence of changes is not recorded. Peptic ulcers are reported in ten cases. This comprises 21.2 per cent of the cases in which the condition of the stomach is mentioned, but only 2.2 per cent of the cases in which autopsy was performed. It is questionable, therefore, that these lesions are of any significance in the genesis of the marked gastro-intestinal disturbances that characterize this disease. In only five cases is the stomach reported as congested, ecchymotic or injected. This does not agree with the frequent occurrence of hemorrhagic congestion seen by Stewart in adrenalectomized dogs. Other lesions are few in number and of varied nature.

TABLE 9.—*Changes in the Gastro-Intestinal Tract in Cases of Addison's Disease*

	Cases
Eosophagus	
Diverticulum	1
Stomach	
Carcinoma	2
Infection	1
Pallor of mucosa	2
Atrophy	1
Ecchymoses	3
Congestion	1
Chronic gastritis	1
Ulcer	7
No change	21
	40
Duodenum	
Ulcer	4
Hyperplasia of Brunner's glands	2
Mammillation of duodenal wall	2
	8
Jejunum, ileum and colon	
Carcinoma of rectum	1
Ascariasis	2
Appendicitis	1
(Tuberculosis discussed above)	
	4

SYMPATHETIC NERVOUS SYSTEM

Addison first regarded the symptoms of the disease that he described, as being the result of destruction of the suprarenal glands. Later, finding that the sympathetic ganglions of the celiac plexus were involved frequently, he suggested that this lesion may be a contributing factor in the production of the syndrome. Following his work, in the older literature, considerable emphasis was laid on the changes in the sympathetic ganglions, and their part in the production of the clinical syndrome. Lewin, in his early statistics, concluded that the symptoms are dependent not only on suprarenal changes but very likely on other changes, particularly in the sympathetic nerves. Von Kahlden [512] in 1891 collected a number of reports of cases and added his own observations, stating that he had found marked changes in the abdominal

sympathetic ganglions. These consisted of atrophy of the ganglions, thickening of the capsule, mild round cell infiltration and hemorrhage. In 1896, von Kahlden [518] reported on fifteen additional cases in which after careful microscopic examination he failed to find changes in the sympathetic ganglions. He concluded that the changes in these structures were of no importance in the production of the clinical picture of Addison's disease. Bramwell [428] in 1897 favored the sympathetic origin of the symptoms of Addison's disease. Bramwell, however, had overestimated the frequency of organic changes in the sympathetic ganglions.

A somewhat modified view is held by Alezais and Arnaud, who asserted that pigmentation could be accounted for only by the involvement of the sympathetic ganglions in the capsule of the suprarenal glands. Laignel-Lavastine and Halbron, in a study of eight cases of tuberculosis of the suprarenal glands, found destruction of the sympathetic ganglions to a marked degree in three cases. The patients in these cases did not show pigmentation of the skin. The authors therefore regarded the involvement of the pericapsular sympathetic nerves as of little importance in the production of the pigmentation of the skin. This is confirmed in a study of six cases of bilateral tuberculosis of the suprarenal glands without clinical symptoms of Addison's disease, the records of which were obtained from the Department of Pathology of the University of Minnesota. In these six cases, marked fibrosis and lymphocytic infiltration of the capsule with involvement of the pericapsular sympathetic nerves was noted. In one case, caseous necrosis involved the pericapsular region extensively.

In 1903, in an anlysis of the available pathologic data, Neusser concluded that the pigmentation, though an important diagnostic feature of Addison's disease, is not an integral part of the disease, but an indirect rather than direct symptom, arising through the agency of local and general disease of the sympathetic system. Also, that the symptoms of Addison's disease are brought about by suppression of the functions of the suprarenal glands by the splanchnic nerves and the celiac ganglions. Neusser based his conclusions mainly on the unfounded assumptions that the sympathetic nervous system controls pigmentation of the skin and that the sympathetic system is dependent on the suprarenal glands for normal nutrition and tone.

From an analysis of cases of atrophy, Bittorf [9] came to the conclusion that morphologic changes in the sympathetic nerves are seldom seen and, when present, are insignificant and in no way influence the symptoms.

From an analysis of the recent literature, changes in the celiac plexus are noted, as in table 10.

It is evident from table 10 that the changes in the celiac plexus are inconstant, and that in the majority of cases the ganglions appear normal. The clinical syndrome is well developed in those cases in which no demonstrable changes are present in the sympathetic ganglions. It is therefore highly improbable that anatomic alterations in these structures have any part in the production of the syndrome. It is more likely that, in the majority of cases, the anatomic changes in the sympathetic nerves are secondary to the changes in the suprarenal glands.

GENITO-URINARY TRACT

The changes in the genito-urinary tract reported in the literature are as given in table 11. The changes are relatively few in number and can be considered only as accidental.

TABLE 10.—*Changes in the Celiac Plexus in Addison's Disease*

Changes	Cases
Tubercle in solar plexus (Baucke)	1
Solar plexus embedded in fibrous tissue and caseous glands (Cullan, 2 cases; Flemming, Lewis and Langmead, each 1)	5
Cretaceous nodules about solar plexus (Finlayson, Withington, Laignel-Lavastine and Porak)	4
Connective tissue increase and round cell infiltration (Wiesel, cases 2 and 4; Aslan, Nicolau and Petresco, Debove, Richon, Skirving and Welsh)	6
Lymphocytitc infiltration (Fahr and Reiche)	1
No chromaffin tissue in solar plexus (Hedinger; Löffler, 3 cases; Wiesel, cases 1 and 3; Crowell)	7
Chromaffin tissue increase (Hedinger)	1
Infiltration by lymphogranuloma (Warthin, Crowe and Jackson)	1
Amyloid deposites (Philpott)	1
No change in celiac plexus (Miller, Crouzon, Pföringer, St. Thomas Hospital report [2 cases], Karakascheff [3 cases], Werdt, Foix, Bendix, Bruno, Conder [2 cases], Steinhans, Green, Langerhans, Bernard and Heitz, Phillips, Schmidt, Simmonds [2 cases], Kreibig, Fahr and Reiche [2 cases], Brenner [2 cases])	27

HEART AND BLOOD VESSELS

Table 12 gives the changes in the heart and blood vessels as recorded in the autopsy reports. As in the kidney, in the heart a number of lesions of varied nature are shown, which may be considered of accidental occurrence. In Furuta's case, the bacterial endocarditis may be considered the primary cause of the suparenal injury. The heart is frequently reported decreased in size and in the condition of brown atrophy. This is, however, by no means constant. Barker compared the heart weight and the body weight in twenty of his cases, using Smith's standard. He found the weight of the heart more than 25 Gm. below minimal normal in seven cases, less than 25 Gm. below the minimal normal in seven cases, within normal but less than average normal in nine cases and within normal limits but more than average normal in two cases. This is most likely due to the marked emaciation and loss of weight of the patient and partly to the decreased amount of work of the heart, owing to the low blood pressure.

ACCESSORY CORTICAL NODULES, COMPENSATORY HYPERPLASIA AND ABERRANT CORTICAL TISSUE

The rôle of accessory cortical nodules, compensatory hyperplasia and aberrant cortical tissue as compensatory mechanisms following the destruction of the suprarenal tissue is of considerable importance. As these are of different origin, they will be considered separately.

TABLE 11.—*Changes in the Genito-Urinary Tract in Addison's Disease*

Changes	Cases
Changes in kidney (nontuberculous)	
Atrophy and congestion	1
Chronic nephritis	2
Interstitial nephritis	2
Amyloidosis	1
Granular atrophy	1
Hyperemia	1
Contracted kidney	2
Glomerulonephritis	3
Pyelonephritis	1
Congestion	6
Nephritis	2
Tubular atrophy	9
Hypernephroma	1
Cloudy swelling	1
Bladder	
Purulent cystitis	1
Genital organs	
Hypoplasia	1
Hydrocele	1
Chronic salpingitis	1
Atrophy of the testes, fibrosis	2
Atrophy of both ovaries	1
Myoma of the uterus	3
Parametrial inflammation	1

TABLE 12.—*Changes in the Heart and Blood Vessels in Addison's Disease*

Changes	Cases
Marked arteriosclerosis	10
Moderate arteriosclerosis	16
Narrowing of the aorta (hypoplasia)	9
Mitral stenosis	4
Verrucous endocarditis	2
Myocardial degeneration	3
Chronic ulcerative endocarditis	1
Pericarditis	3
Endocarditis	2
Fatty degeneration	2
Hypertrophy of the heart	3
Defect in the intraventricular septum	1
Gumma of the myocardium	1
Small heart	19
Brown atrophy	16
Normal heart	42

Accessory cortical nodules or interrenal organs are of embryonic origin. They are composed of small encapsulated rests of cortical cells radially arranged about a central vein. The layers are usually arranged in inverted order. Accessory interrenal bodies are often seen in the region of the suprarenal glands, in that of the celiac plexus, on the surface of the liver, about the genital organs, in the retroperitoneal space along the intermediary line and rarely on the surface of the

kidney. Wiesel [517] stated that accessory suprarenal tissue is present near the suprarenal gland and about the vas deferens in 76.5 per cent of newborn males. Hanau observed nodules along the spermatic veins and sex glands in 5.9 per cent of all children under 5 years of age.

Hyperplasia of these organs in the presence of destructive lesions of the suprarenal glands were described by Kovacs, Hübschmann, Kaiserling, Karakascheff and others. Karakascheff described a case in which there occurred destruction of both suprarenal glands with vicarious hyperplasia of accessory suprarenal tissue in the region of the celiac plexus. Symptoms of Addison's disease were absent, and death occurred as the result of peritonitis. In Kovacs' case 6 there was accessory tissue with tuberculosis of both suprarenal glands. The accessory organs weighed 5 Gm. Kovacs attributed the absence of symptoms to the compensatory action of the accessory nodule. Kaiserling described a case in which the left suprarenal gland was absent. The right was hypoplastic and tuberculous. A large accessory nodule on the left side showed tuberculous involvement. Also a large accessory nodule was present that was free from tuberculosis. This structure was apparently adequate to maintain life for a long period without symptoms of Addison's disease. In Hübschmann's case, three small accessory nodules were found along the spermatic vessels. Both suprarenal glands were atrophied, and similar changes occurred in the accessory nodules. In this case, symptoms of Addison's disease were clearly manifested.

Compensatory hyperplasia occurs not only in accessory cortical nodules, but also in the suprarenal gland itself. It has been shown both in experiments on animals and in observations on autopsy material that the suprarenal cortex is capable of undergoing marked hyperplasia. Mackay and Mackay observed hypertrophy of the cortex in albino rats to the extent of 61 per cent following removal of one suprarenal gland. Morelli and Gronchi and Iwabuki found hyperplasia of the zona fasciculata in rats fed on a scorbutic diet. The latter observed mitotic figures in the cells of the zona fasciculata. In rabbits, Muruta found hypertrophy of the zona fasciculata following a beriberi-like disease. Simmonds,[490] after extirpation of one suprarenal gland in guinea-pigs and dogs, observed hyperplasia of the middle zone of the intact suprarenal gland. This occurred only in young animals.

In man, hyperplasia of one suprarenal gland in the presence of aplasia or destructive lesions in the other is occasionally seen. Simmonds [500] recorded three cases in which hyperplasia of one suprarenal gland resulted from a tuberculous process of the opposite organ, and one case in which the opposite organ was destroyed by an old embolic process. He also observed hypertrophy of one organ as the result of

atrophy of the opposite organ. Hübschmann [150] also observed in an adult a hypertrophy of the right suprarenal gland with atrophy of the left. In Veit's case, symptoms of Addison's disease developed in a woman of 50 in the course of ten days. The right suprarenal gland was hypertrophied and showed a venous thrombus; the left suprarenal gland was missing. Marchetti observed an increase in size of the left suprarenal gland with cystic degeneration of the right. Schnyder described hyperplasia and fatty degeneration of the left suprarenal gland in a man 67 years of age, in whom no trace of the left suprarenal gland could be found.

In primary contracted suprarenal gland, there is found a compensatory hyperplasia of the cortex in the form of small adenoma-like nodules. These were first described by Langerhans and confirmed by Fahr and Reiche, Kiefer, Lucksch, Hübschmann,[150] Kovacs, Kraus and others. In these cases, symptoms of Addison's disease were present, but undoubtedly the fatal outcome was delayed for a long period by the compensatory action of these structures. Less frequently, similar nodules may be seen in tuberculosis of the suprarenal gland (see page 756). These nodules may share in the retrogressive changes in primary contracted suprarenal gland and in suprarenal tuberculosis.

Small aberrant rests of cortical cells are sometimes seen in the region of the capsule of the suprarenal gland. They are frequently observed in primary contracted suprarenal glands and in suprarenal tuberculosis. They usually consist of small clusters of cortical cells and are not encapsulated. Evidence that the chromaffin tissue may undergo compensatory hyperplasia is meager. Wiesel [104] described a case of compensatory hyperplasia of extrasuprarenal chromaffin tissue in the presence of destructive lesions of both suprarenal glands, in which symptoms of Addison's disease were absent. As pointed out by Karakascheff, Wiesel failed to give any importance to the accessory suprarenal tissue which was present in this case and which, Karakascheff held, compensated for the loss of suprarenal tissue. Bloch reported a case of compensatory regeneration of the medullary tissue from sympathetic-formative cells. The questionable nature of this case has already been pointed out.

From the foregoing statements, it is evident that following loss of suprarenal tissue, whether through destructive processes or developmental disturbance, a number of compensatory mechanisms may come into play. These consist principally of hypertrophy and hyperplasia of cortical cells, chiefly of the zona fasciculata, hypertrophy of accessory cortical nodules and regeneration of cortex in the form of adenoma-like nodules and small rests of aberrant cortical cells. In some of these cases, this mechanism is sufficient to maintain life and prevent symptoms of Addison's disease. It is probable that the absence of symptoms in

many cases of bilateral destructive tuberculosis of the suprarenal glands is due to the presence of extrasuprarenal accessory cortical tissue that has escaped detection. In cases of primary contracted suprarenal gland, regeneration in the form of adenoma-like nodules is not sufficient to prevent symptoms of Addison's disease, but it is likely that these nodules may prolong life for a considerable period.

These structures are especially susceptible to injury, as shown in the cases of Kaiserling, Hübschmann, Schnyder, Veit and others. Degenerative changes are frequently found in the adenoma-like hyperplasias occurring in primary contracted suprarenal glands. It is supposed that these structures are rendered more susceptible to infection and injurious substances because of functional strain.

(*To be continued*)

Notes and News

University News, Appointments, Promotions, Resignations, Deaths, etc.—Clay G. Huff has been appointed assistant professor of hygiene and bacteriology at the University of Chicago.

Bruce K. Wiseman has been appointed assistant director of the new department of medical and surgical research recently inaugurated at the Ohio State University under the directorship of Charles A. Doan.

C. C. Okell has been appointed professor of bacteriology in the University College Hospital Medical School, London.

J. W. Miller, resident pathologist in the Charity Hospital of New Orleans, has been appointed pathologist at the Gorgas Memorial Institute and Santos Thomase Hospital, Panama City.

The laboratory staff of the Charity Hospital of New Orleans consists of Rigney D'Aunoy, director; J. L. Bevan and A. M. Zoeller, senior resident pathologists; J. M. Miles and R. A. Robinson, Jr., junior residents, and C. J. Tripoli and Mary T. Demotte, assistant resident pathologists.

G. T. Caldwell, formerly professor of pathology in Baylor University, Dallas, Texas, will resume his former post in the place of Morris L. Richardson, resigned.

At the University of Arkansas, Harvey S. Thatcher has been appointed director of the departments of pathology and bacteriology, Joel Wahlin professor of bacteriology, Emmerick von Haam associate professor of pathology and Alphonse Pirnique associate professor of bacteriology and clinical pathology.

International Criminologic Institute.—It has been proposed to establish an international criminologic institute under the auspices of the League of Nations.

Prevention of Cholera—According to *Science*, the Indian Government has invited F. d'Herelle, R. H. Malone and M. H. Latrivi to study the possibility of preventing cholera by means of bacteriophage.

Society News.—The Society of American Bacteriologists will hold its next annual meeting at the Massachusetts Institute of Technology in Boston, Dec. 29 to 31, 1930.

The second International Congress of Microbiology will be held in Berlin in 1933.

The second International Congress of Comparative Pathology will be held in Paris, Oct. 14 to 18, 1931, during the French colonial exhibition. The general secretary is Dr. Grollet, 7, rue Gustave Nadaud, Paris.

R. R. Spencer, of the U. S. Public Health Service, was awarded the gold medal of the American Medical Association at its annual meeting in Detroit "for original work in preparation of a vaccine for Rocky Mountain spotted fever."

At the last meeting of the American Society of Clinical Pathologists, Kenneth M. Lynch was elected president, H. J. Corper president-elect, Clarence I. Owen vice-president and A. S. Giordano (South Bend, Ind.) secretary-treasurer.

American Journal of Cancer.—By means of the financial support of the Chemical Foundation, New York, a new journal, the *American Journal of Cancer*, will make its appearance at the beginning of 1931, under the editorship of Francis Carter Wood. It will replace the present *Journal of Cancer Research* and will be the official organ of the American Society for the Control of Cancer and the American Association for Cancer Research.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE CIRCULATORY MECHANISM IN ARTERIAL HYPERTENSION. SOMA WEISS and LAURENCE B. ELLIS, Am. Heart J. **5**:448, 1930.

In arterial hypertension, a disproportion must exist between the cardiac output and the peripheral resistance. Such disproportion may develop either because of an increase in cardiac output and velocity of blood flow or because of a change in peripheral resistance. A study of the dynamics of the circulation in thirty patients with hypertension revealed no increase in the cardiac output per minute, the circulating blood volume, the arm to face velocity of blood flow or the mean velocity of the circulation. The calculated volume of blood in the lungs was increased. The peripheral resistance was increased to twice the normal, but the estimated work of the left ventricle was only 41 per cent greater than in normal subjects. The mechanism of the circulation in patients with primary nephritis and secondary hypertension was found to be similar to that in patients with primary hypertension.

PEARL ZEEK.

PAROXYSMAL TACHYCARDIA WITH MYOCARDIAL LESIONS. R. H. MAJOR and H. R. WAHL, Am. Heart J. **5**:477, 1930.

A case of paroxysmal tachycardia is described which, at autopsy, revealed an acute and chronic myocarditis of infectious origin, most marked in the auricular portions of the heart. The portal of entry for the infection was thought to have been the tonsils, which were removed one year before the final attack.

PEARL ZEEK.

HEART STANDSTILL OF VAGAL ORIGIN. A. M. WEDD and D. C. WILSON, Am. Heart J. **5**:493, 1930.

A case is described which exhibited permanent nodal rhythm, with periods of standstill of the whole heart and with a high grade bradycardia. These disturbances of rhythm disappeared temporarily following exercise and the administration of atropine, thus indicating their vagal origin.

PEARL ZEEK.

THE DENSITY OF THE SURFACE CAPILLARY BED OF THE FOREARM. SOMA WEISS and WILLIAM R. FRAZIER, Am. Heart J. **5**:511, 1930.

The number of visible surface capillaries per square unit of forearm skin was found to be essentially the same in persons without demonstrable vascular disease and in patients with arterial hypertension, or arteriosclerosis. Therefore, senile involutionary changes in the skin cannot be explained on the basis of an increase in the radius of cell areas supplied by the surface capillaries.

PEARL ZEEK.

BLOOD VESSELS AS A POSSIBLE SOURCE OF VISCERAL PAIN. W. K. LIVINGSTON, Am. Heart J. **5**:559, 1930.

A mass of evidence is presented, including experimental, clinical, physiologic and pathologic data, to support the theory that in "a number of clinical syndromes" so-called visceral pain is caused by changes in the vascular tree.

PEARL ZEEK.

THE LOCAL AND SYSTEMIC EFFECTS OF ARTERIO-VENOUS FISTULA ON THE CIRCULATION IN MAN. LAURENCE B. ELLIS and SOMA WEISS, Am. Heart J. **5**:635, 1930.

Two cases of traumatic arteriovenous fistula are described. Such injuries may have effects on the general circulation, as well as produce the recognized local phenomena. The former may be: (1) increased heart rate, with immediate slowing on compression of the aneurysm; (2) decreased diastolic arterial blood pressure, with increased pulse pressure; (3) a tendency toward an accumulation of blood in the venous portion of the vascular circuit, with probably an increase in total blood mass; (4) a normal or increased cardiac output, depending on the degree of fistula, and (5) a regional and frequently a generalized arteriolar dilatation.

PEARL ZEEK.

ANTIRACHITIC EFFECT OF WINTER SUNSHINE THROUGH CELOGLASS. THEODORE S. WILDER and CHRISTINE VACK, Am. J. Dis. Child. **39**:930, 1930.

The technic and the results of the exposure of infants to winter sunlight which has passed through Celoglass (cellulose acetate on a wire mesh) are presented. In most of the cases, a sustained rise in the phosphorus-calcium ratio begins within two weeks after the start of the exposure. Roentgenologic examinations reveal a deposition of calcium in the bones in the same length of time. The calcification continues to increase throughout the treatment. The authors conclude that infants and children with rickets can be cured in Boston by exposing them during the winter months to sunshine transmitted through Celoglass.

J. N. PATTERSON.

ANTIRACHITIC VALUE OF WINTER SUNLIGHT IN THE LATITUDE OF 42° 21′ (BOSTON). EDWIN T. WYMAN, PHILIP DRINKER and KATHERINE H. MACKENZIE, Am. J. Dis. Child. **39**:969, 1930.

Additional evidence is supplied by experimentation on rats to substantiate the data contained in the earlier portion of this paper regarding the effectiveness of winter sunlight in Boston in the prevention and in the cure of rickets. Aside from a possibility that the sun's rays are least effective in February, and that a marked increase occurs at the end of March, we do not venture to suggest that quantitative differences have been observed. Undoubtedly, with more detailed experiments the relative antirachitic potency of sunshine in each of the winter months could be plotted.

AUTHORS' SUMMARY.

BLOOD REGENERATION IN SEVERE ANEMIA. G. H. WHIPPLE, F. S. ROBSCHEIT-ROBBINS and G. B. WALDEN, Am. J. M. Sc. **179**:628, 1930.

A liver fraction is described which contains 65 to 75 per cent of the potency of whole liver for production of new hemoglobin in experimental anemia due to hemorrhage. This fraction represents 3 per cent of the weight of the whole liver. Probably a number of active substances are represented in this liver fraction. Inorganic substances are important. Supplementing this liver fraction with iron may increase the total output of hemoglobin. The same thing is true for the feeding of whole liver plus iron, which may give maximal production of hemoglobin in experimental anemia. Supplementing this liver fraction with small amounts of whole liver may increase the total output of new hemoglobin above the level due to the liver fraction alone. These experimental observations will be of greater interest when compared with similar controlled observations in various human secondary anemias. This liver fraction is palatable and can be taken in considerable amounts without clinical disturbance. Reasons are given why liver therapy is so spectacular in pernicious anemia and notably less effective in certain secondary anemias. We urge that liver therapy should not be considered inert in any type of secondary anemia until it has been given a thorough test. All evidence available

points to liver and kidney as supplying the essential factors in most available form for the reconstruction of new hemoglobin and red cells in anemia.

AUTHORS' SUMMARY.

THE EFFECT OF SINGLE MASSIVE DOSES OF LIVER EXTRACT ON PATIENTS WITH PERNICIOUS ANEMIA. MATTHEW C. RIDDLE and CYRUS C. STURGIS, Am. J. M. Sc. **180**:1, 1930.

The observed effect of single large doses of liver extract on patients with pernicious anemia confirms the opinion, expressed by Minot, that the response to liver medication depends rather on the total amount of the active liver principle used during a certain period of time rather than on the amount consumed each day. The active liver principle seems to be used in a quantitative fashion. The magnitude of the reticulocyte response does not appear to be influenced, but the rate appears to be accelerated to a certain extent by the dosage of liver extract. That the administration of a single large dose has an intensely stimulating effect on the hematopoietic tissues of the bone-marrow is indicated by the presence of numerous nucleated erythrocytes and immature leukocytes of myeloid origin in the blood during the first two or three days after the liver extract is given.

JOHN PHAIR.

A TUMOR OF THE ADRENAL GLAND WITH FATAL HYPOGLYCEMIA. HORACE B. ANDERSON, Am. J. M. Sc. **180**:71, 1930.

The case herein reported we feel is unique in that it is the only case we can find with typical symptoms of hypoglycemia in which the only outstanding pathologic condition was a tumor of the left suprarenal gland. There was also congestion of the pancreas and pituitary gland. The symptoms were for a time relieved by the administration of dextrose, but later dextrose failed to relieve the symptoms. Epinephrine hydrochloride was given one or two days before the patient died, without effect. When the blood sugar fell below 0.07, the patient became restless and mentally confused and sweated profusely. The lowest blood sugar was 0.04 per cent.

AUTHOR'S SUMMARY.

STUDIES IN THE ETIOLOGY OF SIMPLE GOITER IN RABBITS. BRUCE WEBSTER and ALAN M. CHESNEY, Am. J. Path. **6**:275, 1930.

Further investigations into the etiologic factors involved in an epidemic of simple goiter in rabbits are reported. A diet which consists almost exclusively of cabbage appears to be the major etiologic factor. Fecal and urinary contamination of food seemingly play no rôle in the present epidemic. The addition of water (either tap or distilled) to the diet exerts no appreciable protective influence against the goitrogenic agent. Iodine, administered orally in quantities of 7.5 mg. per week, will completely protect the animal against the goiter-producing factor. There is no evidence that the minute traces of iodine contained in Baltimore city tap water exert any detectable protective influence. The goitrogenic agent is much more active in winter than in summer. This goiter-producing factor appears to be a nutritional one and may act through the oxidation-reduction systems of the body.

AUTHORS' SUMMARY.

THE SIMILARITY OF THROMBO-ANGIITIS OBLITERANS AND ENDEMIC ERGOTISM. JULIUS KAUNITZ, Am. J. Path. **6**:299, 1930.

Thrombo-angiitis obliterans and ergotism (gangrenous form) occur most frequently in people of the same sex, age and social status. The symptoms and physical signs may be the same in both conditions. The pathologic observations in both may be the same in the earlier stages. The main article of diet in both conditions is rye bread. Ergot is a common infection of all grains, particularly rye, in every continent of the globe.

AUTHOR'S SUMMARY.

INSULIN INACTIVATION BY HUMAN BLOOD CELLS AND PLASMA IN VITRO. S. KARELITZ, S. D. LEADER and P. COHEN, Arch. Int. Med. **45**:690, 1930.

Human blood plasma and human blood cells inhibit the action of insulin in vitro. Blood from diabetic patients and that from patients with purulent infections, serum sickness or leukemia cause greater inactivation of insulin in a given time than does normal blood. This inactivation acts better at a mildly alkaline p_H and is ineffective at p_H 6. After from one to two hours' incubation at from 55 to 60 C., the various kinds of bloods lost their inactivating effect on insulin. The inactivation requires time and is not present when the mixture of blood and insulin is immediately injected into the blood stream of the experimental animals.

From the properties and occurrence of the inactivating substance it is believed that it is an enzyme or an enzyme-like substance.

J. W. LEICHLITER.

PANCREATIC FUNCTION. S. OKADA, K. KURAMOCHI, T. TSUKAHARA and T. OOINOUE, Arch. Int. Med. **45**:783, 1930.

This is one of a series of papers dealing with the secretory function, not only of the pancreas, but of all the digestive glands. In a preceding paper it was shown that hypoglycemia provokes the gastric, pancreatic and biliary secretions, and that hyperglycemia inhibits these by humoral action on the secretory centers, from which the autonomic nervous system transmits the impulses to the acting cells. This phenomenon is given the name of "humoroneural regulation of the secretion of digestive juices." No such mechanism exists for the salivary secretion or for the intestinal secretion.

Amino-acids stimulate the autonomic nervous center and humoroneurally provoke the gastric secretion. Fats also stimulate the centers of the pancreatic and biliary secretions.

When both vagi are severed, the humoroneural regulatory mechanism disappears, so that the importance of the autonomic nervous center and of the vagus nerves for this mechanism is proved.

The hyperglycemia caused by the intraduodenal administration of dextrose thoroughly inhibits the secretory activity of the stomach when a series of test meals is ingested.

J. W. LEICHLITER.

THROMBO-ANGIITIS OBLITERANS (BUERGER). S. SILBERT, A. L. KORNZWEIG and MAE FRIEDLANDER, Arch. Int. Med. **45**:948, 1930.

A study of blood volume by the dye method was made in eighty-seven persons with thrombo-angiitis obliterans, nine persons with atherosclerosis and twenty-two normal persons. An average reduction of 21 per cent in blood volume was found in sixty-nine typical cases of thrombo-angiitis obliterans. This fact suggests that a concentration of the blood is usually present in this disease.

AUTHORS' SUMMARY.

CHANGES IN BLOOD DEXTROSE AND INORGANIC PHOSPHATES AFTER INTRAVENOUS INJECTION OF PARATYPHOID B FILTRATE IN DEPANCREATIZED DOGS. MAUD L. MENTON and HAROLD A. KIPP, J. Infect. Dis. **46**:267, 1930.

In normal dogs, subcutaneous injections of paratyphoid B toxin result in an immediate rise in blood sugar and in inorganic phosphates followed by a return to normal in both constituents in from four to six hours. Large amounts of toxin produce a progressive rise in inorganic phosphates and an early hyperglycemia followed by a fatal hypoglycemia.

In depancreatized dogs, subcutaneous injections of this toxin cause a progressive rise in inorganic blood phosphates together with an early hyperglycemia followed by a fatal hypoglycemia. Large doses of toxin produce a progressive increase in inorganic blood phosphates and a progressive hypoglycemia ending in death.

AUTHORS' SUMMARY.

THE MECHANISM CONTROLLING MIGRATION OF THE OMENTUM. C. B. SCHUTZ, Surg. Gynec. Obst. **50**:541, 1930.

To the previous theories of gravity, intestinal peristalsis, and chemotatic attraction the author adds the following: Peritoneal irritation results in active hyperemia of the omentum. This is followed by serous and cellular exudate, and the vessels lose their tortuosity with resultant gradual spreading out of the omentum in all directions but when it comes in contact with the focus of irritation it adheres to it. The spreading out of the omentum is attributed to the straightening out of the blood vessels due to the increased blood pressure. The omentum, being attached to the arteries, is pulled along.

RICHARD A. LIFVENDAHL.

CAROTENE AND VITAMIN A: THE ANTI-INFECTIVE ACTION OF CAROTENE. H. N. GREEN and E. MELLANBY, Brit. J. Exper. Path. **11**:81, 1930.

Tests on a specimen of carotin (melting point 174 degrees) showed that in growing rats this substance had the property of conferring complete immunity to the development of spontaneous infection. In animals on a diet free from vitamin A and carotin, septic foci invariably developed and the animals died. When carotin was given in the food, the amount of protection conferred on the animals was generally proportional to the amount of carotin eaten. With the basal diet used in these experiments, 0.005 mg. of carotin gave only slight immunity and 0.01 mg. partial immunity, whereas 0.02 mg. and greater amounts gave complete or practically complete immunity.

AUTHORS' SUMMARY.

OVARIAN TRANSPLANTATION. JOHN H. HANNAN, J. Obst. & Gynæc. Brit. Emp. **36**:569, 1929.

Hannan reports the results of his study of ovarian transplantation conducted in two series of rabbit to rabbit, and cat to rabbit, after the recipients had been spayed previously. The site chosen for transplantation was an area bounded by the erector spinal muscle and the last rib; this was preferred because of its rich vascularity, accessibility and the landmarks that render easy the removal of the transplant for study. Removal was done after two, four, six, eight or twelve weeks. There was "a rapid degeneration followed by a total disappearance of all traces of the transplant including necrotic debris. No period was observed in which the ovarian tissue regenerated or even remained stationary in amount; and the degenerative changes, which were observed as early as 14 days after transplantation, progressed steadily throughout the period of survival of the transplant. . . . On the evidence, therefore, the case for ovarian transplantation as a justifiable procedure must fail."

A. J. KOBAK.

THE TOXICITY OF IRRADIATED ERGOSTEROL. J. B. DUGUID, M. M. DUGGAN and J. GOUGH, J. Path. & Bact. **33**:353, 1930.

Viosterol (irradiated ergosterol) is more toxic for rats fed on a synthetic vitamin-free diet of high calcium content than for rats fed on a normal diet of bread and potatoes. In preparing a synthetic diet for use in investigating the toxicity of viosterol, attention must be paid to the calcium content of the diet. Should casein be used in the diet, precautions must be taken to ensure that the calcium content of the casein does not unduly raise the total calcium content of the diet.

AUTHORS' SUMMARY.

VISUALIZATION OF EMBOLUS IN EXPERIMENTAL PULMONARY EMBOLISM. B. MARTIN, Arch. f. klin. Chir. **155**:577, 1929.

The femoral vein in dogs was exposed and compressed; below the compression a solution was introduced consisting of iron chloride 1 cc., 0.9 per cent sodium chloride solution 1 cc. and from 15 to 20 Gm. of barium sulphate. A rapid coagu-

lation of the blood resulted, and on removal of the compression the clot was carried on, while because of the barium its course could be followed accurately by means of the roentgen ray. The method should be of value in experimental study of pulmonary embolism.

THE EFFECT OF AN EXCLUSIVE MEAT DIET FOR ONE YEAR. W. S. McCLELLAN, Klin. Wchnschr. **9**:931, 1930.

The health of two men was not impaired by an exclusive meat diet for one year.

AUTHOR'S SUMMARY.

EXPERIMENTAL CHRONIC COPPER INTOXICATION. F. OSHIMA and P. SIEBERT, Beitr. z. path. Anat. u. z. allg. Path. **84**:106, 1930.

This is a brief report of a small series of experiments undertaken in an attempt to produce hemochromatosis experimentally by chronic copper intoxication, as reported by Mallory. Nine rabbits were given 200 mg. of copper acetate daily by mouth, and three rabbits were given zinc acetate in similar dosage. The duration of the administration varied from 61 to 249 days. The copper content of the livers of the experimental animals varied from 52 to 170 mg. per kilogram of liver, as compared with an average of 6 mg. per kilogram in six normal control rabbits. The liver cells contained much pigment, the amount being greatest in the peripheral zone of the lobules. The pigment was not soluble in alkalies and was not stained by fuchsin. The necrosis of liver cells and the cirrhosis described by Mallory were not observed. Although the authors were not able to reproduce the changes noted by Mallory, they are convinced that Mallory was able to cause hemachromatosis experimentally, but they believe that some unknown factor in addition to copper is concerned in the process.

O. T. SCHULTZ.

EXPERIMENTAL ACUTE ALCOHOLIC GASTRITIS. A. GOTTSCHALK, Beitr. z. path. Anat. u. z. allg. Path. **84**:131, 1930.

To study the early stages of gastritis induced by an exogenous factor and as a contribution to the theory of the Aschoff school that peptic lesions result from the action of gastric juice on living tissue rather than on tissue dead as the result of a vascular lesion, Gottschalk introduced 60 per cent alcohol in a dosage of 20 cc. into the empty stomach in cats by means of a stomach tube. The animals were killed at intervals varying from one-half hour to five days; the stomach was immediately fixed, and submitted to microscopic examination. All of the animals became severely intoxicated from the amount of alcohol used, and as a rule, during the interval between the administration of the alcohol and death, they refused food. The most marked changes were noted in the dependent portion of the fundus. The pyloric portion was markedly contracted, so that a relative protection was afforded this portion of the stomach. Great importance is attached to the fact that the resulting lesions were focal. They occurred usually on the crests of the mucosal folds, but the furrows between the folds did not escape. The earliest change observed was swelling of the epithelium, with localized desquamation of the latter, the desquamation being held to be due to the mechanical action of the swollen epithelium about the area of denudation. The capillaries about the superficial erosions were engorged and contained an increased number of leukocytes, evidence of an active inflammatory reaction. The exposed supporting tissue was also swollen as the result of the action of the alcohol, but was not killed. Death of the exposed connective tissue was caused by the caustic action of the gastric juice, and the injured tissue was digested. In this way there were produced crater-like erosions that might extend down to the muscularis mucosae. Healing occurred by the epithelialization of the defect. The process of healing was identical with that which Konjetzny and Puhl had described for the human stomach. The author therefore concludes that erosions of the human gastric mucosa, from which peptic ulcers may result, are due to damage done to the mucosa from its surface.

O. T. SCHULTZ.

MALE SEX HORMONE. J. FREUD, S. E. DEJONGH, ERNST LAQUEUR and A. P. W. MÜNCH, Klin. Wchnschr. **9**:772, 1930.

The authors have confirmed the existence of a male sex hormone. The growth of the comb of a castrated rooster is used as a test for the presence of the hormone, also that of normal and castrated hens, the diminished involution of the genitalia of adult castrated rats and the increased development of the genitalia of young rats. The male sex hormone specifically affects the comb of the chicken regardless of its sex.

AUTHORS' SUMMARY.

THE SIGNIFICANCE OF THE SKIN IN SALT AND WATER METABOLISM. STEFAN GERÉB and DANIEL LASZLO, Klin. Wchnschr. **9**:775, 1930.

The influence of an injection of hypertonic sodium chloride solution on elimination of sodium chloride in the urine, and the relation of the chlorides of blood and skin were investigated. A considerable amount of the injected sodium chloride is taken into the skin and is retained four hours after the injection. Pituitary causes a marked excretion of sodium chloride in the urine and a diminished, sometimes entirely absent, absorption of sodium chloride by the skin, while the blood chlorine corresponding to the skin blockade at first increases. Because of the increased elimination of chlorine with administration of pituitary, the blood chlorine returns to normal sooner than otherwise. Pituitary seems thus to affect also the extrarenal tissues.

EDWIN F. HIRSCH.

CULTURES OF HUMAN SKIN. KAETHE BÖRNSTEIN, Klin. Wchnschr. **9**:1119, 1930.

Explants of skin from children were cultured in cover glass preparations and in flasks. The 372 cover glass cultures were as follows: skin 108, moles 129, condylomas 66 and embryonal skin 69. The medium was autoplasma or homoplasma from children and young adults, some mixed with chicken plasma and, to some extent, with chicken embryo extract (in a few cultures also with rat and mouse embryo extracts and human placenta extract). Human embryo extract was used only with embryo skin explants. The cultures were made on the surface of the mediums. Skin explants were kept in good living condition for ninety days, in which there was a growth pause of thirty-eight days (in the dark at room temperature). Moles and condylomas grew like skin explants.

EDWIN F. HIRSCH.

LIVER GLYCOGEN AND THE MENSTRUAL CYCLE. C. KAUFMANN and O. MÜHLBOCK, Klin. Wchnschr. **9**:1170, 1930.

The livers of healthy women during menstruation are depleted of glycogen or have less mobile glycogen.

AUTHORS' SUMMARY.

Pathologic Anatomy

DISPLACEMENT OF THE LEFT NIPPLE IN MITRAL STENOSIS. SIDNEY P. SCHWARTZ, Am. Heart J. **5**:344, 1930.

In healthy children and in male adults both nipples are usually on the same level. In patients with mitral disease of the heart, who have had rheumatic fever in childhood, the dynamics of the valvular lesion cause a deformity of the chest in the region of the left half of the sternum and the adjacent second, third and fourth costosternal junctions. Because of this, an upward and outward displacement of the left nipple results. This sign is not present in patients with isolated aortic insufficiency or congenital heart disease. It was present in over 90 per cent of 200 consecutive patients with mitral stenosis examined at the Montefiore Hospital within the last two years.

AUTHOR'S SUMMARY.

COMPLETE OCCLUSION OF BOTH CORONARY ORIFICES. T. LEARY and J. T. WEARN, Am. Heart J. **5**:412, 1930.

Two cases of essential closure of both coronary orifices are reported. The lesions indicated a slowly progressive process that had probably taken at least months to reach the point of essentially complete closure. No evidences of fatty change, myocarditis or repair were found in the heart muscle. The only adequate explanation of the ability of these patients to live and work rests on a belief that the thebesian veins supplied the needed blood.

THE ANATOMIC SUBSTRATUM OF THE CONVULSIVE STATE. WALTHER SPIELMEYER, Arch. Neurol. & Psychiat. **23**:869, 1930.

In so-called genuine epilepsy, the usual lesion described is a loss of ganglion cells in Ammon's horn and a corresponding increase in glia elements. This so-called gliosis is the terminal stage. It differs from what is seen in the early stage of genuine epilepsy. In fresh foci, many ganglion cells are lost, or are replaced by proliferated rodlike cells now known as Hortega's cells, or appear as so-called "ischemic" ganglion cells. These do not stain with the Nissl stain, but stain well with hematoxylin and eosin. The cell body is narrow, and the nucleus is disintegrated. Similar changes — sclerosis, loss of Purkinje's cells, shrinkage of the molecular zone — are present also in the cerebellum. The earliest changes show here as a branchlike network of proliferating glia cells. The fresh changes were observed by Spielmeyer after epileptic seizures and states regardless of the type or cause of the epilepsy. Genuine and symptomatic forms of epilepsy caused similar changes. The etiologic factor — trauma, tumor, Huntington's chorea, etc., did not influence them. In Spielmeyer's opinion, the main cause of the changes is in the vascular disturbances, for he found similar changes in Ammon's horn in a case of tuberculous endarteritis. Here they were caused by an organic obstruction to the circulation. The vascular, vasomotor disturbances, not organic, producing an impediment to the circulation are the cause of the changes in Ammon's horn and the cerebellum in epilepsy. These two organs are singled out because their blood supply is naturally poor.

GEORGE B. HASSIN.

THE EFFECTS OF ANEMIA ON THE CEREBRAL CORTEX OF THE CAT. EDWIN F. GILDEA and STANLEY COBB, Arch. Neurol. & Psychiat. **23**:876, 1930.

Gildea and Cobb tried to study, among other phenomena, the condition of the cerebral ganglion cells in experimental anemia. Young cats were employed, and light ether anesthesia was used while the blood vessels were being exposed and ligatured. The occlusion of the vessels was effected by traction on all ligatures, a procedure which at once produced complete coma. The anemia was considered severe when the tissue in general appeared bloodless and when the animals ceased breathing within from one to two minutes after occlusion of the vessels and had convulsions during the period of occlusion (the ether anesthesia was not deep). The brains were hardened in a diluted solution of formaldehyde, U. S. P. (1:10), and stained with cresyl violet, scarlet red and Hortega's silver carbonate methods. The changes varied according to the length of time the animals survived, duration of the anemia and other factors. The lesions were "areas of devastation" (in animals that survived more than twenty-four hours) in which, owing to cell "necrosis," cells had ceased to be or were abnormal — shrunken, homogeneous, pyknotic, with the nuclei dark, resembling Spielmeyer's ischemic nerve cell change; the oligodendroglia cells were increased; the capillaries became more conspicuous; especially involved were the third and fourth lamina. Other changes showed in the processes that appeared like "icicles" or were swollen (especially in animals that lived from three to eleven days); vacuolated or fat-containing cells were rare; more common was satellitosis. The meninges and the perivascular spaces were usually dilated, with some lymphocytic infiltration and fat globules. Abnormal oligodendroglia were absent. The shrunken cells commonly considered as repre-

senting a chronic lesion were found to show an acute change, while the swollen cells, considered as showing acute changes, are looked on by Gildea and Cobb as manifesting a chronic condition. The conclusions are that the changes though present are "subtle," that none can be considered pathognomonic of cerebral anemia and that ten minutes of cerebral anemia is sufficient to impair cortical cells permanently.

GEORGE B. HASSIN

OCULAR CHANGES IN EXPERIMENTAL BOTULISM. CHARLES M. SWAB, Arch. Ophth. **3**:437, 1930.

In experimental botulism in rabbits the following changes were observed in the nuclei of the third and fourth cranial nerves: round cell infiltration; lymphoid cells packed into parenchyma; extravasation of red blood cells; migration of lymphoid cells; thickening of capillary endothelium; neuronophagia; chromatolysis, satellitosis, necrobiosis, nuclear displacement, nuclear shrinking, vacuolization, powdery granulation of Nissl bodies and complete disintegration of ganglion cells and increase of neuroglia. Similar changes were observed in other parts of the midbrain. The meninges showed small round cell infiltration beneath the ependymal lining of the third ventricle, diffuse round cell infiltration and massive extravasation of erythrocytes into the meninges. The meningeal vessels were distended with red corpuscles. Thrombosis was not frequent in the midbrain. The optic nerve showed focal infiltration in the parenchyma, diffuse increase of neuroglia and round cell infiltration of pial and arachnoidal sheaths. In the optic tract were round cell infiltrations, extravasation of erythrocytes, emigration of lymphoid cells and stagnation of blood. The retina showed fat formation in the ganglion cell layer; pyknosis, chromatolysis and vacuolization of ganglion cells; powder-like reduction of pigment granules; engorgement of vessels with red corpuscles, and stagnation of blood.

CHARLES WEISS.

BONE CHANGES IN HYPERPARATHYROIDISM. E. L. COMPERE, Surg. Gynec. Obst. **50**:783, 1930.

A meaty nodule, 1 by 1¾ cm., reddish, semielastic and smooth, surrounded by a smooth capsule, was removed from the vicinity of the lower pole of the left lobe of the thyroid gland in a woman 59 years of age. Osteoporosis of the calvaria, osteoporosis and bowing of the femurs, thinness of the cortex of the shafts of the long bones, rarefaction of the pelvic bones and sinking-in of the lumbar bones were still present ten months after the extirpation. However, postoperatively the calcium levels of the blood and urine were lowered, the phosphorus was increased to normal, and the general condition of the patient was improved. The clinical syndrome in this patient can hardly be regarded as a compensatory hyperplasia of the parathyroid glands, because another parathyroid gland removed from the same side showed normal structure.

RICHARD A. LIFVENDAHL.

THE ABSORPTION AND TRANSFERENCE OF PARTICULATE MATERIAL BY THE GREAT OMENTUM. G. M. HIGGINS and C. B. BAIN, Surg. Gynec. Obst. **50**:851, 1930.

Graphite particles injected into a subcutaneous pouch of the anterior abdominal wall containing the distal two thirds of the omentum of the cat took the following course: along the mesothelial surfaces, in the histiocytes about the blood vessels of the omentum, and in forty-eight hours from the hepatic ligaments and the lesser omentum to the coronary ligament and then to the central tendon of the diaphragm; from here, by way of the lymphatics on the pleural surface, into the sternal lymph channels and the anterior mediastinal lymph nodes. Thus there are two abdominal drainage systems, the one from the gastro-intestinal tract through the mesentery to the cisterna and the other from the omentum and diaphragm through the anterior mediastinum to the cervical lymph ducts.

RICHARD A. LIFVENDAHL.

FAT NECROSIS OF THE BREAST. G. HADFIELD, Brit. J. Surg. **17**:673, 1930.

Fat necrosis of the breast mimics the clinical signs of carcinoma, in that the overlying skin is adherent and shows the peau d'orange appearance and the lump is hard and in most cases moderately adherent to the underlying tissue. The lesion is most frequently composed of a cystic cavity filled by yellow or brown fluid surrounded by a wall of chalky appearance with lipophages, lymphocytes, multinucleated giant cells containing isotropic crystals, and many fibroblasts in the periphery.

The process is regarded as a slow aseptic saponification of neutral fat by blood and tissue lipase analogous to pancreatic fat necrosis. Some of the forty-five cases recorded occurred after trauma in the form of direct injury or following subcutaneous injections of physiologic solution of sodium chloride or subsequent to radical operations on the breast for carcinoma; in cases of the latter the lesions have been regarded as being a recurrence of carcinoma.

RICHARD A. LIFVENDAHL.

TUBERCULOUS MYOCARDITIS. J. G. THOMSON, J. Path. & Bact. **33**:259, 1930.

In a man, aged 41, the subject of uveoparotid fever (Heerfordt), the following lesions were found post mortem: tuberculosis of the lungs apparently spread by both the blood and the lymph, tracheobronchial and mediastinal glandular tuberculosis and massive tuberculous infiltration of the septum and of the greater part of the wall of the left ventricle of the heart. Microscopically, there was present a tuberculous arteritis, which is suggested as a factor in the wide extent of the lesion.

AUTHOR'S SUMMARY.

ON TUBERCLE FROM INOCULATION OF THE IRIS WITH REFERENCE TO RETICULO-ENDOTHELIAL CELLS. K. ALBRICH, Arch. f. Ophth. **123**:694, 1930.

The author's former experiments on animals confirmed the results of other investigators, showing that the reticulo-endothelial cells have the same significance in the inflammation of the eye as in that of other organs, viz., the ingestion of tissue débris. This they perform as polyblasts (macrophages) and not in their original form. Albrich has watched the transition of histiocytes into macrophages in early foci of tuberculous infections of the iris. He describes the cell arrangement in such foci. This shows to best advantages in the second week of a tubercle bacillus infection in the eye of a rabbit, especially in those cases in which some of the fluid mediums also was introduced into the eye, setting up a severely toxic reaction. The center of this focus consists of white blood cells with lobular nuclei, mostly in the stage of disintegration, and covered with a mantle of carmine-containing polyblasts (macrophages). On the outer edge are numerous elongated histiocytes, provided with offshoots containing a great number of intensely red carmine granules. These cells lie between fibroblasts that are already beginning to proliferate and, approaching the center, change into a zone of larger epithelioid-like cells which still preserve their histiocyte character. Toward the center, as well as within it, are large multiform polyblasts loaded with vacuoles and tissue granules which have completely lost their histiocyte character but still contain pale carmine granules. The process is exactly that found in a conjunctival abscess. The rôle of other cells is not clear, but he found cell pictures that represented the transformation of lymphocyte into monocytoid cells, which would bear out Maximow's theory.

Diffuse inflammations cannot be clearly analyzed as to cell behavior, arrangement and significance; but even in such conditions there are pronounced nodules with caseous nucleus where only polyblasts are assembled in the region of cell detritus.

The author tried to eliminate toxic reaction by using washed bacilli from dry medium. The subjects were white rabbits which had been given a week's prepara-

tory treatment with carmine. If the inoculation takes, the bacilli can be found at any time; in the iris, several hours after infection, and very soon also in the ciliary body. This does not indicate an infection by way of the blood, for the bacilli were introduced into the anterior chamber in much greater numbers. Acute irritation could not be avoided. The author thinks that he has discovered the origin of the carmine-containing cells; morphologically and positionally, they may be adventitial cells. Hence there is no essential difference as regards kind and disposition of cells in the toxic specific inflammation and the specific inflammation with least possible irritation (washed bacilli). The carmine-containing polyblasts are derived from the neighboring iris, where numerous similar cells and histiocytes are found. Their transition into granular tissue is easily followed. The neighboring corneal tissue remains unchanged.

CHARLES WEISS.

LESIONS OF THE PANCREAS IN FATTENED SWINE. J. KUP, Beitr. z. path. Anat. u. z. allg. Path. **83**:64, 1930.

The relatively frequent association of diabetes and obesity has led French writers to speak of a "diabète gras." The amount of interlobular adipose tissue in the pancreas of obese persons may be so great as to warrant the designation of pancreatic lipomatosis. Baló determined an actual diminution in the amount of parenchymatous tissue in the fatty pancreas of the obese, and Truhart found necroses in the interstitial fat of 50 per cent of such pancreases examined by him. The nature of the relationship between such pancreatic changes and diabetes in the obese is not easy to determine. Similar fatty infiltration and fat necroses have been seen in the pancreas of a number of species of domestic animals and especially in swine fattened for slaughter. A variety of domestic swine prepared for market in Hungary appears to be particularly prone to such changes. Kup examined the pancreases of 110 animals of this variety that had been fattened for slaughter and 61 lean animals of the same variety that had not undergone the fattening process. The animals were healthy market swine, and the absence of duodenitis or intestinal catarrh was noted. Multiple necroses were detected in the pancreas of 41.8 per cent of the fattened swine, whereas no necroses were seen in the pancreas of the lean animals. The older and the fatter the animal, the larger was the number of necroses. The author believes the sequence of changes to be as follows: deposition of fat in the interlobular tissue, separation of the pancreatic lobules by adipose tissue, pressure on the lobular ducts, stasis of secretion, ascending infection, focal parenchymatous necrosis, liberation of lipase and focal necrosis of fat. That diabetes is not observed in such swine as the result of the pancreatic lesions is explained by the short life of the fattened animal.

O. T. SCHULTZ.

VITAL STORAGE IN THE CONNECTIVE TISSUE IN LOCAL ACTIVE HYPEREMIA AND INFLAMMATION. N. KUSNETZOWSKY, Beitr. z. path. Anat. u. z. allg. Path. **83**:649, 1930.

The vital storage of colloid substances by the cells of the reticulo-endothelial system is influenced by a number of extracellular factors, in addition to factors inherent in the cells. Among these extracellular factors are: the path of administration of the material, whether intravenous, subcutaneous or intraperitoneal, the material being stored in largest amounts by those cells with which it first comes in contact; the mechanics of the local circulation of the various tissues and organs, and the degree of dispersion of the colloid material. The last named factor makes itself manifest in differences in the storage of a finely dispersed material like trypan-blue and a coarsely dispersed one like india ink. The author has previously published the results of experiments undertaken to study the effects of local active hyperemia and inflammation on the vital storage of trypan blue. The present contribution presents the results of similar experiments with india ink. Rabbits were used. To cause local hyperemia, a part of the hind leg was encased in a copper jacket through which water at a temperature of 46 to 48 C. was circulated

for a period of forty minutes. Twenty minutes after the beginning of the application of heat, dilute india ink was injected into the ear vein. The skin and subcutaneous tissue of the warmed area, similar tissues from the corresponding area of the opposite leg and portions of the internal organs were removed at varying intervals and subjected to microscopic examination. Local aseptic inflammation was set up by implanting in the subcutaneous tissue of a limb or in the intermuscular tissue of the abdominal wall bits of sterile sponge. In some experiments, the sponge was saturated with turpentine. In other experiments, local inflammation was produced by cauterization of the skin. India ink was injected intravenously during the acute stage of the inflammation or at varying intervals thereafter. The tissues were removed for microscopic examination at varying periods after the injection of the carbon suspension. Local active hyperemia caused the early deposition of conglutinated carbon particles on the inner surface of the endothelium of the capillaries and venules of the hyperemic tissues. A similar condition was not seen in the control tissues. The material was attached to the surface of the endothelial cells and was not stored by them, the author disagreeing with those who maintain that ordinary endothelium has the property of phagocytosing carbon particles. The material did not pass through the capillary walls and was not seen in the extracapillary tissues. When the tissue was removed at longer intervals after the injection, most of the particles of ink had been removed from the surface of the endothelium and had been transported elsewhere by the blood stream. In local inflammatory tissues, the observations were much the same as in hyperemia if the tissue was removed in the early stages of the inflammatory process. The carbon particles adhered to the inner surface of the capillary endothelium, but were not engulfed by the latter and did not pass out into the surrounding tissues. Even during the early stage of active leukocytic emigration, little carbon was seen outside the vessels. As the latter became more permeable, however, the carbon particles made their way through the walls of the vessels and were taken up by the polyblasts in the tissues outside the vessels. A transformation of endothelium into polyblasts was never seen by the author. India ink stored in polyblasts that had come to rest in the scar tissue could be seen at prolonged periods after the acute stage of the inflammation. If the india ink was injected during the later, healing stages of the inflammatory process, carbon particles stored in polyblasts could also be seen in the extravascular connective tissue, but the amount was much less than if the injection was made during the acute stage. The storage of carbon by the cells of the extravascular tissue of an inflamed area depends apparently on the degree of permeability of the vessels caused by the inflammation. Trypan blue passes through the vessels much more readily than do the relatively coarse particles of india ink.

O. T. SCHULTZ.

ECHINOCOCCUS CYST OF THE VERTEBRAL COLUMN. G. GERLACH, Centralbl. f. allg. Path. u. path. Anat. **47**:112, 1930.

A man, 59 years old, suffering from a transverse myelitis in the region of the eleventh thoracic vertebra, died of ascending cysto-ureteropyelonephritis. At necropsy, an echinococcus cyst, 5.5 cm. by 5 by 1, was found in the body of the eleventh thoracic vertebra, compressing the spinal cord. Nineteen years previously the man had been operated on for a similar cyst of the left side of his back at about this level, but not until seven years before his death did any evidences of compression of the spinal cord appear.

GEORGE RUKSTINAT.

A PAPILLOMA OF THE PULMONARY VALVE. H. WEBER, Centralbl. f. allg. Path. u. path. Anat. **48**:49, 1930.

In a man 38 years old dying four days after developing symptoms of pneumonia of the left lower lobe, a papillary mass, 11 by 6 by 5 mm., was found on the front pulmonary cusp, 2 mm. to the right of the nodule of Arantius. From serial sections it was decided the mass originated from the subendocardial connective tissue.

GEORGE RUKSTINAT.

TUBERCULOUS SPLENOMEGALY. G. LEIDEL, Centralbl. f. allg. Path. u. path. Anat. **48**:54, 1930.

Leidel thinks that the four types of tuberculous splenomegaly suggested by Lubarsch, namely, indurated, hemorrhagic, diffuse miliary and large nodular, should be supplemented by a tumor-like granulating form.

GEORGE RUKSTINAT.

WERLHOF'S DISEASE. G. GERLACH, Centralbl. f. allg. Path. u. path. Anat. **48**:81, 1930.

Gerlach reports extensive studies of the organs of a 14 year old girl dying from essential thrombocytopenia. There were extensive hemorrhages into the kidney pelves, ovaries and serous membranes and hemorrhagic infarction of the auricles. From studies of the bone-marrow the disappearance of platelets seemed ascribable to marked alterations of the giant cells of the bone-marrow. These varied from one to ten times the size of a myelocyte and had nuclear changes, such as mulberry-like contours and clumping of chromatin.

GEORGE RUKSTINAT.

PECULIAR GROWTH ON THE CRANIUM FROM TRAUMA. W. SCHELLENBERG, Frankfurt. Ztschr. f. Path. **38**:319, 1930.

On the cranium of a man, aged 76, was a crateriform growth the inner margin and cavity of which was formed by remnants of periosteum. Below the periosteum, between the outer and inner tables, was a pale red, homogeneous connective tissue containing bone splinters and fragments. There was a history of trauma to the head some twenty-six years earlier, and the growth is interpreted as the result of fracture of the external table followed by growth of connective tissue with central shrinking.

CHOROIDITIS ALBUMINURICA. A. FUCHS, Zentralbl. f. d. ges. Ophth. **22**:785, 1930.

The author discusses the various choroiditic pigmentation centers that occur in nephritis and nephrosclerosis, as well as in retinitis albuminurica. These include the small peripheral discolorations, large retinochoroiditic foci, the black foci with paler margin that lie peripherally described by Elschnig, and the beadstring pigmented streaks described by Siegrist. Fuchs made histologic examination of such a black retinochoroiditic focus in a patient in whom the Elschnig and Siegrist types of foci were present simultaneously. Usually albuminuric choroiditis has a different cause than albuminuric retinitis, viz., arteriosclerosis and periarteritis; the causative agent of albuminuric retinitis is not known. The choroiditic foci have a great significance in cases of nephritis and nephrosclerosis — they show the poor condition of the choroidal vessels and the serious condition of the patient. In the discussion of this paper, Pascheff reported a case of choroiditis serosa during pregnancy. The patient's symptoms disappeared without treatment after delivery.

CHARLES WEISS.

THE STRUCTURAL CHANGES IN METHYLALCOHOL-AMBLYOPIA. A. E. MACDONALD, Zentralbl. f. d. ges. Ophth. **22**:791, 1930.

Reports are made on material from three cases of methylalcoholic poisoning with symptoms of blindness apparent before death. The central scotoma and blindness are due to the toxic degenerative changes which the ganglionic cells undergo. The changes that arise later and that lead to optic atrophy are due to the progressive degeneration of the nerve fibers, the result of the lesion of the ganglionic cells. Ganglionic cell changes in other parts of the body are not as pronounced as those in the eye; the effect of light falling directly on the ganglionic

cells in the retina may play a distinctive rôle. Further observations are necessary. Injection of formaldehyde into the cavity of the eye should be made immediately after death, and investigation of fatty degeneration proximal to the point of exit of the optic nerve in the retinal portion is recommended.

CHARLES WEISS.

Pathologic Chemistry and Physics

HYDRION CONCENTRATION AND EDEMA IN PERFUSED HEARTS OF RABBITS. J. M. ORT and J. MARKOWITZ, Am. J. Physiol. **94**:60, 1930.

Perfusion experiments with Ringer-Locke's solution of varying hydrogen ion concentration on excised hearts of rabbits indicated that there were many points in common between such isolated but working tissues and simple hydrophilic colloids, as the former, like the latter, showed increased imbibition in conditions of increased acidity.

H. E. EGGERS.

PLASMA PROTEINS. H. J. WIENER and R. E. WIENER, Arch. Int. Med. **46**:236, 1930.

The two fractions of the serum protein, the albumin and globulin and the plasma fibrinogen together with other blood constituents significant of the clinical condition have been determined in diabetes mellitus, benign glycosuria, localized and generalized infections, diseases of the liver and the gallbladder and in renal conditions. The methods used and the physiologic concentrations determined by these methods are stated. The plasma proteins are within the physiologic limits in diabetes mellitus and in benign glycosuria. In infections the albumin is decreased, slightly in mild cases and decidedly in the more severe infections. The fibrinogen is increased, even in slight infections which do not call forth an increased globulin concentration. In the more severe infections the globulin is increased, and the increase parallels the severity of the condition. In cirrhosis of the liver the albumin is decreased and the globulin is increased. The changes in the serum protein concentrations, however, are not so marked as in the infectious conditions. The fibrinogen is a low normal or decreased. In jaundice without elevation of temperature, the serum proteins are normal or increased, the albumin is generally within the normal limits and the globulin is increased. The fibrinogen remains within the normal limits. In cholecystitis and in jaundice due to the use of arsphenamine the picture is similar to that found in infections. In chronic, glomerular nephritis, in the absence of an infection, the serum proteins are slightly reduced, especially the albumin fraction. The fibrinogen is often slightly increased. In acute nephritis the changes found are the same as in infections. In nephrosis the albumin is materially decreased, the globulin is normal and the fibrinogen is much increased. The significance of the changes in the protein concentrations and their bearing on questions of site of formation, port of entry and functions are discussed. The importance of complete chemical analytic studies and the recognition of complications which may mask the results expected from the pathologic condition studied are evidenced. The difference in relationship of globulin to fibrinogen in infections and disturbed hepatic function is pointed out. The diagnostic and prognostic value of changes in the albumin-globulin quotient and in the globulin-fibrinogen quotient is discussed.

AUTHORS' SUMMARY.

POSTMORTEM BLOOD CHEMISTRY IN RENAL DISEASE. S. H. POLAYES, E. HERSHEY and M. LEDERER, Arch. Int. Med. **46**:283, 1930.

From a postmortem study of the creatinine and urea contents of the blood specimens in 100 cases, the following conclusions may be made: 1. Blood creatinine determinations are often helpful as an aid in determining the status of the renal function during life. 2. The urea values are not as helpful as the creatinine

figures. 3. A creatinine content of 4 mg. or more per hundred cubic centimeter of blood obtained post mortem indicates marked creatinine retention during life and therefore severe renal insufficiency.

AUTHORS' SUMMARY.

FIXATION OF A METAL IN INFLAMED AREAS. VALY MENKIN, J. Exper. Med. **51**:879, 1930.

Colloidal iron or ferric chloride injected into the inflamed peritoneal cavity is fixed in the cavity and fails to reach the retrosternal lymphatic nodes, whereas, in the absence of inflammation, iron accumulates in these nodes and becomes demonstrable by the Prussian blue reaction. Quantitative studies show that after intraperitoneal injection of ferric chloride the retrosternal lymphatic nodes of animals with normal peritoneal cavities contain approximately 56 per cent more iron than do the nodes of animals with inflamed peritoneal cavities. Ferric chloride injected into the circulating blood enters an inflamed area in the skin, and the inflamed tissue gives the Prussian blue reaction. Quantitative determinations show that the amount of iron in inflamed areas is much greater than that found in inflamed areas of animals that have received no iron.

AUTHOR'S SUMMARY.

THE BLOOD CHEMISTRY OF AN ACUTE TRYPANOSOME INFECTION. RICHARD W. LINTON, J. Exper. Med. **52**:103, 1930.

The carbon dioxide capacity of the serum is markedly lowered early in infection with *Trypanosoma equiperdum*. The nonprotein nitrogen and uric acid constituents of the blood are increased in the terminal stages. The kidneys also show terminal degenerative changes. The cholesterol remains unchanged throughout. Lecithin is markedly increased, most of the observations showing a 20 to 50 per cent rise in this substance. Liver glycogen is lower than normal in the early stages and could not be demonstrated in the later stages of the infection. The blood sugar remains normal until a very late period in the disease.

AUTHOR'S SUMMARY.

CHANGES IN THE SPINAL FLUID FOLLOWING INJECTION FOR SPINAL ANAESTHESIA. A. H. IASON, M. LEDERER and M. STEINER, Surg. Gynec. Obst. **51**:76, 1930.

Comparison of the spinal fluid before and twelve hours after spinal anesthesia showed a polymorphonucleosis as high as 800 per cubic millimeter in eleven of thirty-one cases. In twenty instances there was an increase in the sugar content varying from 7 to 135.2 per cent. There was no change in the albumin, globulin or colloidal gold curves. No correlation was present between the occurrence of postanesthesia sequelae and the changes observed in the spinal fluid.

RICHARD A. LIFVENDAHL.

BLOOD PHOSPHORUS IN HEALTH AND DISEASE. H. D. KAY, Brit. J. Exper. Path. **11**:148, 1930.

In normal human blood, the usual methods of analysis show no detectable quantity of nucleic acid phosphorus in the red cells. In cases of disease in which there is a marked increase above normal in the percentage of reticulocytes in the blood, small, but quite definite, amounts of nucleic acid phosphorus, roughly proportional in quantity to the extent of the reticulocytosis, have been demonstrated. It may be concluded that, whatever the nature of the reticulum itself, the reticulocytes occurring in such diseases probably contain nucleic acid, and may therefore be looked on as red cells from which the whole of the nuclear material has not been extruded.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

THE INFLUENCE OF SURFACE TENSION ON THE GROWTH OF THE TUBERCLE BACILLUS. FRANK B. COOPER, Am. Rev. Tuberc. **21**:354, 1930.

No optimum surface tension was noted at which growth was more profuse or more rapid than on an untreated medium. Progressively increasing amounts of sodium soap of castor oil with the accompanying decrease in surface tension caused a corresponding inhibition of the rate of growth. Throughout the range of surface tension of from 72.4 to 35.4 dynes, growth was always at the surface of the medium and in typical pellicle formation. There was never any indication of growth beneath the surface.

H. J. CORPER.

THE INFLUENCE OF UNSATURATED FATTY ACIDS ON THE VIRULENCE OF TUBERCLE BACILLI. G. PLATONOV, Am. Rev. Tuberc. **21**:362, 1930.

Fats of the unsaturated type act bacteriolytically, retard the growth of tubercle bacilli and lower their virulence. Guinea-pigs, inoculated with tubercle bacilli the virulence of which has been lower under the action of unsaturated fats, develop a chronic tuberculous process of fibrous character, and show increased resistance to subsequent reinfection. The parenteral therapy of tuberculosis, consisting of the introduction of various preparations of unsaturated lipoids, deserves serious attention and study. Acids with high iodine value should be assigned a place of honor in the dietary regimen of the tuberculous patient.

H. J. CORPER.

EXPERIMENTAL TUBERCULOSIS BY INTRACEREBRAL INOCULATION. WILLIAM H. FELDMAN, Am. Rev. Tuberc. **21**:400, 1930.

By the intracerebral method of injection the resistance of many of the mammals to bacilli of tuberculosis of avian origin is but relative and such animals as dogs and guinea-pigs, which are usually considered to be refractory to infection with avian bacilli of tuberculosis, may develop well defined disease, when the infectious agent is introduced by this route. There is evidence that the disease develops with much greater rapidity when the infection is induced intracerebrally as compared to the intravenous or subcutaneous routes of inoculation. The pathologic process induced by the intracerebral injection of virulent bacilli of tuberculosis is essentially a specific monocytic proliferation. The lesions in the brain appear to originate in the perivascular tissues and most frequently involve the pia mater. They extend into the sulci, and occasionally focal lesions may occur in the substance of the cerebrum. When the infectious material is introduced into the brain, lesions may develop in distant organs; the liver and spleen are sites of predilection. The lungs are less frequently involved and in none of the experimental animals that received intracerebral injections were definite lesions demonstrated in the kidneys. In two instances the intracerebral injection of bacilli of tuberculosis of human origin into chickens resulted in the formation of well defined meningeal lesions in the brain. The intracerebral method of inoculation offers many interesting possibilities in experimental tuberculosis and should be worthy of trial in the demonstration of the causative micro-organism that may be difficult or impossible to demonstrate by other means.

H. J. CORPER.

FOOD POISONING BY STAPHYLOCOCCI. E. O. JORDAN, J. A. M. A. **94**:1648, 1930.

Strains of staphylococci of diverse origin and cultural character may generate in broth a substance that causes gastro-intestinal disturbances when given by mouth. This substance is destroyed by boiling and is destroyed or weakened by being heated at from 60 to 65 C. for thirty minutes.

BACTEREMIA DUE TO SALMONELLA SUIPESTIFER. S. E. BRANHAM, L. J. MOTYCA and C. J. DEVINE, J. A. M. A. **94**:1758, 1930.

Salmonella suipestifer was isolated from the blood of a patient in an acute febrile condition. Most frequently human infections with this organism have presented the clinical picture of gastro-enteritis (food poisoning) or pneumonia.

SYPHILIS IN NEGROES IN MISSISSIPPI. P. S. CARLEY and O. C. WENGER, J. A. M. A. **94**:1826, 1930.

The examination of 7,228 blood specimens from an unselected group of rural Mississippi Negroes above the age of 9 years by complement fixation tests for syphilis showed positive reactions in 19.3 per cent of all males and in 18 per cent of all females examined. The rates of infection in the various age groups reach a maximum between the ages of 30 and 39 for both males and females. It is pointed out that the positive results probably represent less than the actual amount of syphilis in the group. The infection rates in this unselected group are roughly the same as those discovered at the United States Public Health Service Venereal Disease Clinic at Hot Springs, Ark., in a selected group who were seeking medical aid for previously diagnosed venereal disease. These data suggest that, from a public health and economic point of view, syphilis is probably the major public health problem among rural Mississippi Negroes today.

AUTHORS' SUMMARY.

TORULOSIS OF CENTRAL NERVOUS SYSTEM. F. B. SMITH and J. S. CRAWFORD, J. Path. & Bact. **33**:291, 1930.

A case is recorded, in a woman, of fatal granulomatous infection of the brain and spinal cord by a yeastlike micro-organism, probably *Torula histolytica*.

AUTHORS' SUMMARY.

THE GENUS WILLIA. J. F. D. SHREWSBURY, J. Path. & Bact. **33**:393, 1930.

Three species of *Willia* and a variety of one of these species have been observed under various conditions of artificial cultivation over a period of about eighteen months. The general conclusions reached from this study are as follows: The genus can be identified by the following characters: (1) the giant colony growth on a standard medium such as malt agar at room temperature; (2) the surface film growth on aqueous fruit extracts; (3) the sporulation characters, the optimum mediums for sporulation being either carrot or prune agar; (4) the absence of mycelium. *Willia* possess only feeble proteolytic and saccharolytic powers, but are able to produce aromatic ethers in mediums containing sugars. The genus is indivisible, although *Willia saturnus* (Carlsberg) differs from the other two species studied in its cultural and sporogenic characters. *Willia anomala* (Chapman) and *Willia belgica* (Chapman) are closely related organisms, and are possibly varieties rather than separate species, although the ascospores of the latter yeast, as observed in the present study, are not certainly pileate. *Willia* are not pathogenic for man or for the laboratory animals, and their presence in human morbid material is merely accidental.

AUTHOR'S SUMMARY.

"INFLUENZAL" ENCEPHALITIS. J. G. GREENFIELD, J. Path. & Bact. **33**:453, 1930.

Two cases of acute disseminated encephalomyelitis following "influenza" are described. One was fatal five days and one seven weeks after the onset of symptoms. The lesions found in the nervous system were of the same kind as in the encephalomyelitis which sometimes follows vaccination, smallpox and measles. These cases are considered to support the view that acute disseminated encephalomyelitis is a disease per se, which may be brought on or directed against the nervous system by certain febrile or exanthematous diseases.

AUTHOR'S SUMMARY.

EXPERIMENTAL VACCINIAL ENCEPHALITIS. E. WESTON HURST and R. W. FAIRBROTHER, J. Path. & Bact. **33**:463, 1930.

Vaccinial "encephalitis" can be readily transmitted from rabbits to monkeys by the intracerebral inoculation of virulent material; the resulting reaction, which is primarily meningeal, is figured and described. No definite evidence has been obtained that the vaccinia virus, after intradermal inoculation and subsequent general dissemination, is capable of exciting an encephalitis, even when a mild trauma is at the time of vaccination or subsequently inflicted on the nervous system. The histology of postvaccinial encephalitis in man is totally different from that of cerebral vaccinia in the rabbit or the monkey; it is highly improbable that the virus of vaccinia plays a direct part in the causation of the former condition. The reaction of the central nervous system to the vaccinia virus is to be sharply differentiated from that to the poliomyelitis virus, etc., in that the one is primarily mesodermal, the other primarily ectodermal; the virus of vaccinia is not neurotropic in the same sense as that of poliomyelitis.

AUTHORS' SUMMARY.

VACCINIAL ENCEPHALITIS. J. MCINTOSH and R. W. SCARFF, J. Path. & Bact. **33**:483, 1930.

Virulent strains of vaccinia can produce in rabbits a definite meningo-encephalitis after intracerebral, intravenous and intradermic inoculation. The lesions produced are strictly comparable with the visceral lesions in rabbits and with those of postvaccinial and postvariolar encephalitis in man.

AUTHORS' SUMMARY.

OCULAR INFECTION OF RABBIT WITH SPIROCHAETA CUNICULI. A. KLARENBEEK, Ann. de l'Inst. Pasteur **44**:201, 1930.

The inflammatory reaction in the cornea produced by inoculation of *Spirochaeta cuniculi* into the anterior chamber of the rabbit's eye is similar to that from inoculations of *Spirochaeta pallida*. The cornea of the rabbit, however, is more resistant to the first organism. It is not easy to get an infection of the cornea after either superficial or deep scarification. On the contrary, the inoculation of *Spirochaeta pallida* into the intact conjunctival sac gives rise to a typical reaction of the cornea. The scleral conjunctiva, on the other hand, and especially the skin of the upper lid are more sensitive to *Spirochaeta cuniculi* than the cornea. Several times a primary syphilitic lesion in the skin or in the conjunctiva of the rabbit has followed cutaneous or subcutaneous inoculation of the upper eyelid. This sensitivity may serve to differentiate the two varieties of spirochetes.

CHARLES WEISS.

UNIVERSAL SCLEROSING TUBERCULOUS LARGE CELL HYPERPLASIA. K. MYLIUS and P. SCHÜRMANN, Beitr. z. Klin. d. Tuberk. **73**:166, 1929.

On the basis of clinical and anatomic observations of two cases and of reports in the literature, a particular type of tuberculosis is described. The histologic entity of this type of tuberculosis is usually a miliary focus of large cell hyperplasia which does not caseate, the only form of retrogressive alteration of which is a hyaline sclerosis. The clinical course is always chronic. The following clinical varieties belong to this type of lesions: the benign miliary lupoid of the skin (Boeck), the lupus pernio, the multiple cystoid tuberculous ostitis (Jüngling), the multiple spina ventosa of adults (E. Fraenkel), a tumor-like, noncaseating tuberculosis of the lymph nodes (Walz), an endurating form of pulmonary tuberculosis (von Gebsattel), a noncaseating tuberculous splenomegaly (von Bebsattel and M. Askanazy), and a type of ocular tuberculosis, which is first described in the present paper. The localization of the lesion varies greatly. The paper is illustrated with good photomicrographs.

MAX PINNER.

THE INFLUENCE OF LIPOID SOLUTIONS ON THE GROWTH OF ACID-FAST BACILLI. T. NYRÉN, Beitr. z. Klin. d. Tuberk. **73**:238, 1929.

A large variety of acid-fast organisms were grown on mediums containing various lecithins and cholesterin. Lecithin promotes the growth of tubercle bacilli; cholesterin does not. Tubercle bacilli from cold-blooded animals and acid-fast saprophytes are not influenced by lecithin. All acid-fast bacilli produce strongly granulated forms on lipoid mediums. The addition of peptone promotes the growth of all acid-fast bacilli, with the exception of true tubercle bacilli.

MAX PINNER.

THE COURSE OF HUMAN TUBERCULOUS INFECTION. P. SCHÜRMANN, Beitr. z. path. Anat. u. z. allg. Path. **83**:551, 1930.

This is the second part of an extensive and intensive study of human tuberculous infection as encountered in 1,000 successive unselected necropsies on persons dying at all ages. The study was undertaken for the purpose of testing the validity of Ranke's hypothesis that tuberculous infection runs a fixed cyclic course, the succession of stages of which depends on four modes of spread and three allergic phases. The first part of the study (previously abstracted) dealt with those cases in which the spread and generalization of the infection occurred chiefly by the hematogenous and lymphogenous paths. The present study is based on 387 cases, in which the spread was by what may be termed paths of excretion. It is a study of chronic pulmonary tuberculosis, the essentials of which are the softening and caseation of an older focus and its rupture into the bronchial system, with a spread of the infectious material within the lung by way of the bronchi. These two modes are not necessarily isolated manifestations of the infection in any given case. On the contrary, they usually occur together, but one predominates over the other. Thus, the person with a generalized infection that runs a protracted course may develop a pulmonary phthisis, in which the spread is along the bronchial system. Conversely, the person with chronic pulmonary tuberculosis may exhibit undoubted evidence of the hematogenous spread of the infection, such as isolated tubercles in distant organs, or a terminal miliary tuberculosis or tuberculous meningitis. Although one mode of spread may influence, to a certain degree at least, the pathologic process resulting from the other mode, it is in the concomitance of the two modes of spread that the author finds his chief argument against the acceptance of Ranke's hypothesis. The latter he holds to be based on theoretic conceptions and not on demonstrable anatomic facts. He also can find no morphologic basis for Ranke's three allergic phases. This part of Ranke's doctrine is also held to be highly speculative.

O. T. SCHULTZ.

INFLUENCING THE SUSCEPTIBILITY OF MICE TO SPIROCHAETA GALLINARUM INFECTIONS BY BLOCKING THE RETICULO-ENDOTHELIAL SYSTEM. A. PENTSCHEW, Centralbl. f. allg. Path. u. path. Anat. **47**:1, 1930.

Pentschew found that he could increase the time during which *Spirochaeta gallinarum* was found in the blood by first giving mice intravenous injections of india ink, iron saccharate, and colloidal preparations of gold, silver, and bismuth. Copper preparations were too toxic. Presumably, these chemicals acted either by mechanically burdening the reticulo-endothelial system by a toxic effect on the mice or by a combination of these factors. Injections of colloidal or soluble bismuth preparations seemed therapeutically inert once a spirochetal infection was established. Secondary injections of colloidal silver rendered the blood spirochete free within from six to twelve hours.

GEORGE RUKSTINAT.

INVOLVEMENT OF THE SALIVARY GLANDS IN GENERALIZED MILIARY TUBERCULOSIS. E. KIRCH, Centralbl. f. allg. Path. u. path. Anat. **48**:12, 1930.

The salivary glands in six of nine bodies of patients who died of miliary tuberculosis were involved in the disease process. The bodies were of eight males and one female from 19 to 22 years of age. Nine parotids were examined and only one showed miliary tuberculosis; of thirteen submaxillary glands six were diseased, and of six sublingual glands, two. Usually, only one definite tubercle was found and this was almost invariably located in the parenchyma rather than in the interstitial tissue or capsule.

GEORGE RUKSTINAT.

ASCARIASIS AND SUPPURATIVE PLEURITIS. E. JENNY, Schweiz. med. Wchnschr. **60**:266, 1930.

A suppurative pleural effusion that contained eggs of arscarides developed on the right side in a boy, aged 16 months, who had ascariasis. In the course of three months the boy recovered completely. The development is explained as follows: Ascarides entered the liver by way of the choledochus. On the surface of the liver they caused an abscess, which perforated through the diaphragm into the pleural cavity. But it is also possible that the pleural ascaris invasion resulted from a lung stage in the development of the parasites.

BARTONELLA CANIS (A NEW CAUSE OF ANEMIA). W. KIKUTH, Zentralbl. f. Bakteriol. **113**:1, 1929.

Kikuth describes a new cause of anemia in dogs which belongs to the *Bartonella* group and is named *Bartonella canis*. The parasites are well stained only by the Giemsa stain and are coccoid and rod forms which sometimes resemble *Bartonella bacilliformis* and sometimes *Bartonella muris*. They pass Berkefeld —N filters. In normal dogs they cause a slight infection which quickly becomes latent but can be activated by splenectomy. Splenectomized dogs infected with *Bartonella canis* develop progressive anemia, acute or chronic, which frequently leads to death. All attempts to cultivate the parasites have been unsuccessful. Transmission of the disease by fleas has also been unsuccessful. The administration of neoarsphenamine leads quickly to a disappearance of the parasites from the peripheral blood and to complete healing of the infection.

PAUL R. CANNON.

FILTRABLE FORMS OF TUBERCLE BACILLI. E. MOROSOWA, Zentralbl. f. Bakteriol. **113**:200, 1929.

The author describes experiments in testing the filtrability of tubercle bacilli from tuberculous material and from cultures. No tuberculous lesions were found in guinea-pigs into which injections of the filtrates had been made. Morosowa suggests that the important factors in this type of investigation are the kinds of filters used, the filtration pressure and the reaction of the material filtered. Finer pored filters must also be used before one can conclude that filtrable forms of tuberculosis exist.

PAUL R. CANNON.

MENINGITIS CAUSED BY INFLUENZA BACILLUS. STRUNK, Zentralbl. f. Bakteriol. **113**:429, 1929.

Two cases of primary meningitis in nurslings caused by *Bacillus influenzæ* are described. There were no clinical evidences of influenza, but a pure culture of influenza bacilli was obtained from the spinal fluid in each case. In one case, the organisms were also found in the brain, the middle ears and the lungs. The organisms were unusually pleomorphic, and were always strongly hemoglobinophilic.

PAUL R. CANNON.

Immunology

INTRARENAL ARTERIAL TUBERCULIN INJECTIONS IN NORMAL AND TUBERCULOUS MONKEYS, GOATS AND SWINE. ESMOND R. LONG, CHARLES B. HUGGINS and ARTHUR J. VORWALD, Am. J. Path. **6**:449, 1930.

Distinct renal allergic responses were secured on the injection of tuberculin protein into the renal arteries of tuberculous monkeys, goats and swine. The allergic nature of the response was established by the fact that similar injection into normal controls did not cause injury (except such as occurred from vascular occlusion). In the monkeys the lesion produced was purely degenerative, in the goats chiefly degenerative but occasionally inflammatory, and in the swine degenerative and of a more inflammatory character than in the goats. The inflammation in the goats and swine took the form of an interstitial nephritis. The glomerular changes observed in a former investigation in which larger dosage of tuberculin protein was used, were not produced. The intensity of renal tuberculin reaction did not parallel the intensity of cutaneous reaction in this series of animals.

AUTHORS' SUMMARY.

BRUCELLA AGGLUTININS AND BRUCELLINE ERYTHEMA IN VETERINARIANS. T. FOREST HUDDLESON and H. W. JOHNSON, J. A. M. A. **94**:1905, 1930.

Of forty-nine practicing veterinarians, twenty-eight had *Brucella* agglutinins in the blood, but only three gave a history of undulant fever. The results indicate a rather low degree of pathogenic power of *B. abortus*. Veterinarians have observed a peculiar erythema on the skin of the arm following contact with the vagina of cows that have aborted. The erythema comes out on the lateral surface of the forearm in about twenty minutes. Intradermal injection of *Brucella* culture filtrate caused local reaction with constitutional symptoms in veterinarian with history of this erythema, indicating hypersensitiveness to *Brucella* protein.

INFLUENCE OF COMPLEMENT ON SENSITIVENESS OF COMPLEMENT-FIXATION TESTS FOR SYPHILIS. LEON C. HAVENS and FANNIE MAE FRANK, J. Infect. Dis. **47**:100, 1930.

The sensitiveness of complement-fixation tests for syphilis can be increased by closer adjustment of the complement to the conditions of the test. Titration of complement with the addition of inactivated human serum yields a smaller unit than when the serum is omitted, owing to the presence of a thermostabile constituent which can be removed by absorption with yeast. Tests of 1,066 serums, the unit of complement obtained by titration with serum and antigen being used, yielded 45 positive results which were negative with the standard test. Agreement between the complement-fixation test, the serum unit being used, and the Kahn precipitation test was 99.4 per cent, as compared with 95 per cent agreement when the standard Kolmer test with the full unit of complement was used. In 106 treated patients with syphilis, 29 positive results were obtained with the standard test, 61 with the serum unit and 65 with the Kahn precipitation test.

AUTHORS' SUMMARY.

ANTIBACTERIAL FUNCTIONS OF MUCUS. N. E. GOLDSWORTHY and H. FLOREY, Brit. J. Exper. Path. **11**:192, 1930.

The authors review the literature of the lytic substance "lysozyme" and its importance in natural immunity. Lysozyme has been shown to be present in the tears, saliva and intestinal and nasal mucosa of various animals, and even in some of the members of the vegetable kingdom. Further experiments are reported on the variation in concentration of lysozyme in different portions of the gastroenteric tract of certain animals. There appears to be no logical explanation for

these variations from a standpoint of natural immunity. The saliva seems to be the most constant source of lysozyme in all animals except the goat. However, not all air organisms and few pathogens are inhibited by lysozyme.

ALFRED M. GLAZER.

VIRULENCE, IMMUNITY AND BACTERIOLOGICAL VARIATION IN RELATION TO PLAGUE. A. S. BURGESS, J. Hyg. **30**:165, 1930.

Experiments to determine the prophylactic efficacy of agar-grown vaccine, broth-grown vaccine and carbolized spleen pulp vaccine on African pouched rats inoculated with small doses of plague culture are described. The agar-grown vaccine gave a survival rate of 25 per cent, the broth-grown vaccine, 56 per cent and the carbolized spleen pulp vaccine, 75 per cent. However, the carbolized spleen pulp vaccine is not likely to be of practical value because of its difficult preparation and the undesirable local effects it produces.

Experiments are then described in which the virulence of *B. pestes* was reduced by passage through immune or partially immune rats, and then increased by passage through normal rats. High temperatures also decrease the virulence of the organism. No direct correlation between type of colony and virulence of the organism is found.

ALFRED M. GLAZER.

ANTIVACCINIAL SERUM. C. H. ANDREWES, J. Path. & Bact. **33**:265, 1930.

Vaccinia virus could be recovered from a mixture with excess of immune serum, even when the mixture had stood for four days at room temperature or for twenty-four hours at 37 C. Nevertheless, carefully controlled experiments showed that with prolonged contact, virus was progressively more and more difficult to recover. This suggests that a stable antigen-antibody union may occur in vitro but that it is certainly not complete for some days. This idea is considered in relation to the fact that antibody is apparently effective in vivo in the course of a few minutes.

AUTHOR'S SUMMARY.

SPECIFIC ANTIBODY ABSORPTION BY THE VIRUSES OF VACCINIA AND HERPES. WILSON SMITH, J. Path. & Bact. **33**:273, 1930.

Vaccinial and herpes testicular emulsions are capable of absorbing their homologous antibodies from immune serums. The specificity of absorption is shown by cross absorption experiments in which vaccinia testis failed to absorb out any herpes antibodies and herpes testis failed to absorb out any vaccinial antibodies; also by the fact that each virus will select for absorption its homologous antibodies from a mixed serum. Vaccinia testis emulsion, in which the virus has been destroyed by heating at 58 to 60 C. for one hour, shows greatly reduced power of antibody-absorption.

AUTHOR'S SUMMARY.

THE INHERITANCE OF THE BLOOD GROUP FACTORS. G. K. KIRWAN-TAYLOR, J. Path. & Bact. **33**:313, 1930.

The results of the present investigation are without exception in agreement with Bernstein's theory of inheritance; the greater part of the work was carried out without knowledge of Bernstein's theory. Taken with the very large number of cases collected by Furuhata they show that the theory of triple allelomorphs may be accepted with considerable safety. It must be admitted that exceptions have been recorded, and the possibility of errors in these cases has already been considered. It is conceivable, however, that some discordant results are capable of another explanation. Although Bernstein's hypothesis admits of only one possible formula for group 1 bloods ABBa, it is perhaps possible for mutations to occur in this grouping so as to give rise to zygotes having the formulae AB and aB. Should such a "sport" arise, the probability would be that the AB zygote would

be fruitless owing to the doubling of the dominants, and only the aB zygote capable of reproduction. Such a possibility would result in a return to von Dungern and Hirszfeld's original views as to the possible offspring of matings concerning a group 1 individual. Even therefore if there is some reluctance to accept Bernstein's theory of inheritance as definitely proved, there is an enormous amount of data in support of the conclusion that no child can possess in its blood (Lattes 1929) an agglutinable substance which is not present in one of the parents. The possible medicolegal applications are obvious.

AUTHOR'S SUMMARY.

THE RÔLE OF THE SPLEEN IN THE PRODUCTION OF ANTIBODIES. W. W. C. TOPLEY, J. Path. & Bact. **33**:339, 1930.

These experiments, as a whole, would seem to lend further support to the view that the spleen is concerned, not only in the fixation of antigen, but in the elaboration either of antibody itself, or of some intermediate product.

AUTHOR'S SUMMARY.

MORPHOLOGY OF IMMUNITY REACTIONS OF VASCULAR ENDOTHELIUM. W. EWALD, Beitr. z. path. Anat. u. z. allg. Path. **83**:681, 1930.

The importance of humoral reactions in immunity and in the protection of the body against infection has long been recognized. The importance of participation of the true reticulo-endothelial system in such immunity and protective reactions, especially as related to the formation of soluble immune substances and to the phagocytosis of invading organisms, also appears well established. In recent years, Oeller, Siegmund, Domagk, Hammerschmidt, and others have ascribed to the ordinary vascular endothelium phagocytic activity and other important properties that are of the greatest importance in the defense of the organism against acute infection. They have claimed that the participation of the endothelium is demonstrable morphologically. To proliferation of periadventitial cells and to perivascular infiltration about the smallest vessels, some of the more recent writers have ascribed an equally important rôle in subacute and chronic infections. In his investigation of the reactions manifested by vascular endothelium in acute infection, Ewald used the strain of *Corynebacterium murisepticum* that had been employed by Hammerschmidt, who had considered this organism especially suited to calling forth the endothelial reactions described by him as evidence of the participation of the endothelium in the defense of the host. At frequent intervals following injection of mice the leukocytes of the blood were counted and blood smears were examined to detect the occurrence of phagocytosis. Beginning with the eighth hour after injection, the animals were killed at intervals of from two to four hours and tissues taken for microscopic study. Injection of the bacteria was followed by moderate leukocytosis for from twelve to eighteen hours. During the next eighteen to twenty-four hours the leukocytes decreased to about 4,000 per cubic millimeter, and underwent a still further decrease to 1,500 and less during the terminal hours of the infection. Clumps of agglutinated bacteria could be detected in the blood at about the twenty-fourth hour, but phagocytosis was not observed until forty hours after infection and later. At a much earlier period than this, namely from the twenty-fourth hour on, phagocytosis of the clumped bacteria by the reticulo-endothelial cells of the liver and spleen was evident. The morphologic endothelial changes described by others were not seen. Ewald concludes that the most important and the most immediately available protective weapons against infection are the humoral and cellular mechanisms of the blood. These lead to agglutination of the bacteria, which process is preparatory to the phagocytosis of the bacteria by the leukocytes and by the reticulo-endothelial cells of the liver and spleen. His experiments offered no support to the view that phagocytosis of bacteria by ordinary vascular endothelium is important or to the view that there occur in the endothelium morphologic changes that may be interpreted as indicating a participation of such endothelium in the immunity reactions of the body.

O. T. SCHULTZ.

AN APPARENT O-GROUP IN A CHILD OF AN AB-PARENT. E. WORSAAE, Klin. Wchnschr. **9**:938, 1930.

The author found the conditions stated in the title and absorption experiments showed that the child had small quantities of A receptor. Subsequent tests demonstrated agglutination by a high titer A serum. The agglutination test alone is insufficient to exclude a definite receptor, but must be checked by an absorption test.

AUTHOR'S SUMMARY.

THE MECHANISM OF IMMUNITY AGAINST TUBERCULOSIS IN RATS. I. J. GOLDENBERG, Ztschr. f. Tuberk. **55**:125, 1929.

Although rats have a strong resistance against tuberculous infection, tubercle-like lesions can be demonstrated in them following inoculation of bacilli. The extent of these lesions depends on dosage, site of infection and on the strain and age of the rats. The histologic picture of these tuberculoid structures is atypical. Epinephrine and blocking of the reticulo-endothelial system with trypan blue diminishes the resistance of rats. Avitaminosis depresses the resistance markedly. Infected rats do not react to tuberculin.

MAX PINNER.

THE PRECIPITATION REACTION FOR ACTIVE TUBERCULOSIS. H. SCHULTE-TIGGES, Ztschr. f. Tuberk. **55**:133, 1929.

This test is less reliable than complement fixation. It is less frequently positive in favorable forms of active tuberculosis. It is more frequently negative in far advanced cases. Its practical value is limited. Complement fixation combined with red cell sedimentation is preferable.

MAX PINNER.

RESULTS OF BCG INOCULATIONS IN AMSTERDAM. M. R. HEYNSIUS VAN DEN BERG, Ztschr. f. Tuberk. **55**:401, 1930.

The oral administration of BCG to two hundred sixty infants showed that the procedure is harmless, according to an observation over four years. There does not seem to exist any parallelism between skin allergy and immunity. The tuberculosis mortality during the first two years of life in children who had a positive Pirquet reaction within the first year of life was 6.2 per cent in the inoculated group, as compared with 52.3 per cent in the noninoculated group.

MAX PINNER.

IMMUNIZATION WITH SAPONIFIED TUBERCLE BACILLI. A. V. JENEY, Ztschr. f. Tuberk. **55**:496, 1930.

Tubercle bacilli were saponified in a vacuum with concentrated alkali. This antigen had a demonstrable immunization effect on guinea-pigs. Guinea-pigs that were treated with this antigen showed marked cirrhotic processes, particularly in the liver. Evidence is presented to show that the cirrhotic processes are produced by soaplike substances.

MAX PINNER.

THE PERMEABILITY OF THE INTESTINES IN GUINEA-PIGS FOR VIRULENT TUBERCLE BACILLI AND FOR THE BACILLI IN THE BCG VACCINE. A. SAENZ, Ztschr. f. Tuberk. **56**:131, 1930.

Guinea-pigs that received from 1 to 5 mg. of virulent tubercle bacilli by mouth became allergic to tuberculin from thirty to fifty days after the infection. Guinea-pigs similarly infected with from 10 to 20 mg. BCG became sensitive to tuberculin from fifty to eighty days after the infection.

MAX PINNER.

THE INTRACUTANEOUS IMMUNIZATION OF RABBITS WITH BACTERIA AND ERYTHROCYTES. HANS GROSS, Zentralbl. f. Bakteriol. **113**:452, 1929.

Gross finds that good agglutinating and hemolytic serums may be obtained in rabbits by intracutaneous injections. Living, toxic cultures have a better antigenic effect than killed or less virulent strains. Good results were obtained with typhoid and paratyphoid organisms, poorer with dysentery and coli bacilli, and none with staphylococci and pneumococci.

PAUL R. CANNON.

Tumors

THE INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG. PAUL D. ROSAHN, Am. J. M. Sc. **179**:803, 1930.

The postmortem incidence of primary carcinoma of the lung is steadily increasing, and this increase is real and absolute. Combined statistics show that from 1910 to 1919 primary carcinoma of the lung was disclosed in 0.44 per cent of autopsies, and comprised 4.39 per cent of all cancers at autopsy. Since 1920, primary carcinoma of the lung has been found in 0.89 per cent of autopsies and has comprised 6.98 per cent of all cancers at autopsy. Primary carcinoma of the lung is not as rare as was formerly believed. Because of its increased frequency, the clinician should give this disease serious consideration in differential diagnosis in patients of the carcinomatous age presenting puzzling lung symptoms and signs. An early diagnosis will permit accurate prognosis, and in selected cases, perhaps, surgical therapy.

AUTHOR'S SUMMARY.

EFFECT OF ROENTGENIZATION ON CEREBELLAR MEDULLOBLASTOMAS. PERCIVAL BAILEY, Am. J. Path. **6**:125, 1930.

These tumors are composed of embryonic undifferentiated cells of neuroepithelial origin; they grow with extreme rapidity and are sensitive to irradiation, but after a time the cells appear to become radioresistant, according to assumption. Cases are now reported in which persistent irradiation was practiced after removal of the main tumor, without any local recurrence, and in which, nevertheless, the patients died from intraspinal or intracranial extensions. It is assumed that the cells may become scattered into the arachnoid fluid during operation; hence radiation should be applied to the entire cerebrospinal system after operative removal of these tumors.

LYMPHOSARCOMA, WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM. CHARLES DAVISON and JOSEPH J. MICHAELS, Arch. Int. Med. **45**:908, 1930.

Twenty-six patients with lymphosarcoma admitted to this institution since 1922 were investigated, seven of whom presented neurologic signs and symptoms. Four of these patients showed signs of compression of the spinal cord. The literature on this subject reports only one case. In none of the cases was there a direct invasion of the brain or of the spinal cord. The symptoms were due chiefly to compression from invasion of the skull, vertebrae or meninges. Invasion of the cranial cavity took place only when the cervical lymph nodes were involved, and, as observed in our series, involved early. Deep roentgen and radium therapy, while not a cure for the disease, causes some relief from the symptoms during the first few applications. The relief is due chiefly to the recession of the tumor which causes compression on the respective organs. When these enlargements fail to respond to treatment, improvement in the symptoms may not be expected. For a time, however, these patients benefit a great deal by deep roentgen or radium therapy, and at present these are the best forms of palliative treatment.

AUTHORS' SUMMARY.

HEMANGIOMA OF THE UTERUS. E. HORGAN, Surg. Gynec. & Obst. **50**:990, 1930.

There are twenty cases of hemangioma of the uterus in the literature, and of these there are three of the true cavernous type, to which the author adds one. The anterior wall of the uterus contained a typical cavernous hemangioma with an aperture in one of the caverns, allowing the escape of blood into the uterine cavity. From the age of 19 to her present age of 46 years, the patient has had six severe hemorrhages. Differentiation must be made from hemangiomatous fibromyoma and telangiectatic hemangioma in the pelvis.

RICHARD A. LIFVENDAHL.

STRUCTURE AND HISTOGENESIS OF PRIMARY CARCINOMA OF THE LIVER. F. ORSÓS, Beitr. z. path. Anat. u. z. allg. Path. **84**:33, 1930.

For the two types of primary carcinoma of the liver that he believes it possible to distinguish Orsós prefers the names malignant hepatoma and malignant cholangioma. He precedes his minute, detailed and profusely illustrated descriptions of three examples of the former and one of the latter by a brief description of the regenerated liver cells in a case of acute degeneration and atrophy of the liver. The malignant hepatoma arises from small interlobular bile ducts and forms epithelial tubular structures like those of the embryonic liver. Such structures by differentiation lead to the formation of cell cords with bile canaliculi and even of small pseudolobules. The blood vessels are like the sinusoids of the normal lobule, and the stroma is relatively slight in amount. The epithelial cells may exhibit functional bipolarity, in that the portion of the cell next to the vessel may store fat, whereas the portion next to the lumen of the canaliculus may secrete bile. The malignant hepatoma grows expansively, does not infiltrate peripherally and does not invade the lymph channels. It metastasizes by the blood vessels. The tumor may have a multicentric origin, especially in cirrhotic livers. The malignant cholangioma arises from larger interlobular ducts, the characteristics of which it tends to reproduce. The amount of stroma is greater. The tumor infiltrates peripherally, invades the lymph channels and metastasizes by the latter. Bile formation does not occur in the tumor tissue. Transition forms occur, however, between the two tumor types and may be seen in the same tumor. The cholangioma described was unusual in that the stroma was sarcomatous. The author does not consider the tumor a sarcocarcinoma or a mixed tumor, but a combination neoplasm in which the epithelial and mesenchymal elements arose independently of each other.

O. T. SCHULTZ.

THE VALUE OF THE MALIGNANCY INDEX IN THE PROGNOSIS OF TUMORS. S. P. REIMANN, Beitr. z. path. Anat. u. z. allg. Path. **84**:266, 1930.

In the Kaufmann Festschrift number of Ziegler's Beiträge, Reimann discusses briefly the facts that speak against the practical value of any scheme of grading the malignancy of tumors that is based on supposed quantitative variations in the morphology of neoplasms. To test the validity of such a system of grading malignancy, 100 carcinomas of the mammary gland operated on at the Lankenau Hospital in Philadelphia were divided into three prognostic groups. The histologic characters taken into account in the classification were the size and staining reactions of the tumor cells, the proportion of mitoses, the architecture of the tumor, the invasion of lymphatics and blood vessels and the reaction of the stroma. The prognosis thus arrived at was compared with the actual prognosis, as determined by a follow-up of the cases. The former was wrong in 50 per cent of the cases. Reimann concludes that a prognostic classification based on a mathematic grading of histologic characters is not much better than the impression of the degree of malignancy that the experienced pathologist receives from his usual examination of histologic preparations of tumors.

O. T. SCHULTZ.

EXTRATESTICULAR CHORIONEPITHELIOMA WITH GYNEKOMASTIA. W. H. SCHULTZE, Beitr. z. path. Anat. u. z. allg. Path. **84**:473, 1930.

Schultze reports a chorionepithelioma that arose in a retroperitoneal teratoma, and claims it is only the second recorded example of this kind of tumor in the male the origin of which in an extragenital teratoma has been definitely proved. It is the seventh case of extragenital chorionepithelioma in the male and the third example of retroperitoneal chorionepithelioma in the male. The patient was 22 years old. Seven months before his death, he began to complain of pain in the region of the kidney. Three months before death, the breasts began to enlarge. Seven weeks before death, metastases were detected in the lungs roentgenologically, and colostrum could be expressed from the hypertrophied breasts. He lost weight rapidly. The tumor was retroperitoneal and extended from the diaphragm to the sacral promontory. It contained two kinds of malignant tissue, chorionepithelioma and medullary carcinoma, which had metastasized independently of each other to various organs. The chorionepithelioma metastasized chiefly to the lungs, the carcinoma to other organs and especially to the right testis, which had been atrophic as the result of hernia. Spermatogenesis was absent in the left testis. The primary tumor contained squamous epithelium and cartilage. The glandular portion of each breast was 5 cm. in diameter and 1.5 cm. thick. Histologically, the mammary tissue revealed acinar hyperplasia and active secretion. Schultze disagrees with Hertzenberg, who had claimed that the gynecomastia associated with chorionepithelioma is due to a circulating placental hormone derived from the tumor. Schultze maintains that gynekomastia is never associated with tumor formation unless there is damage to testicular function.

O. T. SCHULTZ.

TUBULAR AND SOLID TESTICULAR TUMORS OF THE OVARY. R. MEYER, Beitr. z. path. Anat. u. z. allg. Path. **84**:485, 1930.

Meyer describes seven tumors of the ovary that he considers to be atypical members of the tumor group termed by Pick in 1905 testicular tubular adenoma of the ovary. The first of the neoplasms is like two previously reported by Meyer, in that much of the tissue had the characteristic, well differentiated tubular structure of the adenoma described by Pick, but contained also atypical carcinomatous areas. In the remaining tumors, the deviation from the tubular character was greater and the tumors contained solid carcinomatous areas, portions of sarcomatous morphology, sometimes tissue similar to that of interstitial cell tumors and sometimes areas that resembled granulosa cell tumors. All, however, contained atypical tubular structures that lead Meyer to consider them members of the testicular ovarian tumor group. It is not necessary to derive such tumors from an ovotestis. Meyer believes that they may arise from indifferent ambivalent cell material that in its proliferation to form a tumor may differentiate into male or testicular tissue. He holds it conceivable that twin tumor forms, composed of both ovarian and testicular elements might arise from such indifferent cells. The testicular ovarian neoplasms, for which Meyer proposes the name andreioblastoma, cause varying degrees of virilism of the adult woman. The degree of change toward the male side in Meyer's series was inversely proportional to the degree of differentiation of the tumor tissue. The changes noted were deepening of the voice, hirsutes of the male type and alterations of the sexual psychology.

O. T. SCHULTZ.

METABOLISM OF LEUKEMIC LYMPHOCYTES. E. PESCHEL, Klin. Wchnschr. **9**:1061, 1930.

Leukocytes, especially exudate cells, under aerobic conditions hydrolyze sugar into lactic acid. In contrast, Peschel noted that leukemic lymphocytes have a pure oxidation metabolism, and aerobically are not glycolytic. The leukemic cells are not tumor cells, according to their metabolism, but rather normal young tissue cells.

EDWIN F. HIRSCH.

CONGENITAL MALIGNANT NEOPLASM OF THE LIVER DISSEMINATED THROUGH THE PLACENTA. F. PARKES WEBER, E. SCHWARZ and R. HELLENSCHMIED, München. med. Wchnschr. **77**:624, 1930.

A woman, 38 years old, with diffuse and subcutaneous melanotic tumors became pregnant, and at cesarian section an apparently normal child with melanotic lesions in the placenta was delivered. At 8 months, the child was admitted to the hospital with an enlarged liver and a progressively developing cachexia. It died in the eleventh month from the same condition as the mother. This is said to be the first report of tumor metastasis of mother through placenta and thence to fetus.

A. J. KOBAK.

Medicolegal Pathology

THE DEMONSTRATION OF GONOCOCCI IN SPOTS FOR MEDICOLEGAL PURPOSES. H. LORCH, Dermat. Wchnschr. **89**:1358, 1929.

Gonococci may be demonstrated in dried spots of secretion after weeks and months by maceration in acidified distilled water followed by staining with the combined Neisser-Gram-Pappenheim method.

DETERMINATION OF AGE OF BLOOD SPOTS. SCHWARZACHER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:119, 1930.

In the determination of the age of blood spots, several factors have to be considered, such as the mode of development of the blood stain, the absolute amount of blood present, the thickness of the bloody area and the physical qualities of the object on which the blood spot is found. The action of heat, light and humidity is also of importance. Micro-organisms and fungi may rapidly destroy a blood spot because of their fermentative action. Under ordinary circumstances, the oxyhemoglobin and reduced hemoglobin are gradually transformed into methemoglobin, hematin and other products, which cause a change in the color and a decrease in the water solubility of the blood spot. One notices, therefore, that an originally dark red blood spot appears first brownish red, then brownish or brownish violet, at last exhibiting a dirty gray tint. On transparent objects, one can spectroscopically determine the various hemoglobin derivatives. But the changes in color through aging of the blood spot can also be observed with a photometer (Pulfrich). The solubility of a blood spot is best studied by the use of distilled water; a definite amount of dried, old blood, dissolved within a definite period of time, can then be calculated by colorimetric or refractometric methods. The action of light is the main factor that influences the character and the rapidity of the aging process of a blood spot.

E. L. MILOSLAVICH.

USE OF POWDERED SERUM-GLOBULIN FOR BLOOD GROUPING. P. SEREBRJANIKOFF and M. LEITSCHICK, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:125, 1930.

Since fluid serum cannot be preserved permanently, the authors succeeded in preparing a serum-globulin powder which they recommend as a standard dried serum, mainly for purposes of determinations of blood groups. The amount of ammonium sulphate necessary to precipitate globulins varies for any given serum, and it is impossible to state individually its quantity in advance.

E. L. MILOSLAVICH.

DIFFERENTIATION BETWEEN HUMAN AND ANIMAL HAIR. ADALBERT SCHRODER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:127, 1930.

Various technical procedures for examination of the cuticula are discussed, and a new method, consisting of the printing of hair on the gelatin layer of a photographic plate, without destruction of the hair, is described. The entire length

of a hair should always be examined, as different structural changes occur in various portions of the same hair. There are no differences between the cuticular structure of human hairs taken from various regions of the body. The hairs of a cat and of a dog are easily determined, while those of cattle, horses and goats are difficult to differentiate. From the shape of the cuticula cells, one is unable to distinguish between a hair of a cat and that of other domestic animals. On account of the large variety of races, the hair of dogs shows greater differences in structure than that of cats. The cuticula cells in horses, cattle, goats and deer exhibit a comparatively simple arrangement. The latest work of Litterscheid and Lambardt is analyzed at length and many of their important statements relating to diagnosis of hair are contradicted. One is able to differentiate positively between a human and an animal hair by a study of the cuticula in the entire length of the hair. The cuticular structure (narrow, wavy lines) found in the basal portion of a human hair is present only at the apical end of an animal hair. In examining hairs in their entire length, human hair can be positively identified by its delicate surface structure; the hair of a deer by an absence of such a structure in the apical third. The hairs of dogs and cats can be differentiated from those of horses, cattle and goats because elongated cell forms are not present in the hair of the latter animals. However, it is impossible to distinguish between a hair of a dog and that of a cat, due to the great similarity in their structure. The same is true in trying to differentiate separately between the hair of horses, cattle and goats. If one examines only a part of a hair, a definite diagnosis is impossible. Should the examined section of hair disclose the presence of elongated cellular forms, one can only deduct that it is hair of a cat or a dog.

E. L. Miloslavich.

Bulbar Paralysis Following Injections of Cocaine-Epinephrine. E. Schutt, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:149, 1930.

A man, aged 65, received injections of a 3 per cent procaine hydrochloride solution containing epinephrine for the extraction of teeth, four times within six weeks. He suddenly commenced to show the clinical picture of bulbar paralysis. An almost identical case was described by Heinemann. It is assumed that epinephrine might have increased the blood pressure, leading to a rupture of the small atheromatous vessels within the medulla oblongata, or that the injected drug produced a spasmodic contraction of the blood vessels with subsequent ischemia and gradual necrosis of the corresponding medullary structures.

E. L. Miloslavich.

Fracture of the Epistropheus. H. Dürck, München. med. Wchnschr. **76**:1406, 1929.

A laborer, aged 26, who fell down a flight of stairs while carrying a tub on his back, was able to work for three days thereafter, although he experienced difficulty in moving his neck; chills and fever developed. Because of pain in the right side of the head a mastoid operation was performed and a thrombosed sigmoid sinus discovered. Thereafter the right jugular vein was ligated near its bifurcation, and subsequently the right eye was enucleated because of a purulent panophthalmitis. Death occurred forty-two days after the accident, and at autopsy a partially healed fracture of the right arch of the epistropheus was found. The bone fragment was displaced to the spinous process of the third cervical vertebra and was carious. The presumed course of events was a fracture of the epistropheus, followed by a hematoma which became infected and led to thrombosis of the jugular vein. The process extended to the right arm and resulted in multiple abscess formation in both the pulmonary and the systemic circuits because the patient had a patent foramen ovale.

In a second case reported by Dürck, the fracture involved the dens of the epistropheus of a girl, aged 18. In this case death occurred shortly after the patient had injured her neck while dancing. At autopsy the upper portion of the dens

was adherent to the ligamentum transversus atlantis. The inferior surface showed evidences of a healed fracture, and subsequent dislocation of this part of the dens had caused myelitis. A history of injury to the neck at the age of 11 years explained the unusual postmortem picture on a basis of an epiphyseal separation of the dens.

GEORGE RUKSTINAT.

"GOLDEN HAIR." F. KNUTSSON, Acta radiol. **11**:78, 1930.

The roentgen examination of the skull of a man, aged 34, showed in the scalp many fine threadlike shadows, a few millimeters in length and of metallic density. These shadows were distributed closely over the area where the hair grows. The patient had been bald since his nineteenth year, and in 1918, about 2,000 tufts of hair on gold threads had been inserted into the scalp, but these hairs disappeared completely within the next six months. The golden roots remained.

Technical

A NEW INTERPRETATION OF THE VAN DEN BERGH REACTION. HIRAM F. SNIDER and JOHN G. REINHOLD, Am. J. M. Sc. **180**:248, 1930.

The type of direct van den Bergh reaction observed in serum depends on the concentration of bilirubin. In the cases here reported an immediate van den Bergh reaction was associated with a high icterus index and a delayed van den Bergh with a low icterus index. The van den Bergh reaction changed from negative to delayed, then to biphasic, and finally to immediate as increasing amounts of bilirubin were added to human serum. Dilution of a jaundiced serum with normal serum changed the van den Bergh reaction of the former from immediate to delayed. The temperature of the reacting materials was shown to be an important factor.

AUTHORS' SUMMARY.

SILVER STAINING OF THE ENDONEURIAL FIBERS OF THE CEREBROSPINAL NERVES. GEORGE F. LAIDLAW, Am. J. Path. **6**:435, 1930.

The endoneurium consists of longitudinal fibers and a closely fitting argyrophil web. The distribution of the web is described together with the silver technic necessary for its demonstration.

AUTHOR'S SUMMARY.

A FURTHER MODIFICATION OF DEL RIO-HORTEGA'S METHOD OF STAINING OLIGODENDROGLIA. WILDER PENFIELD, Am. J. Path. **6**:445, 1930.

The method described here has been found particularly useful in staining the oligodendroglia of the retina, nerve head and optic nerves. Microglia is also stained with varying success by this method.

AUTHOR'S SUMMARY.

RETICULUM: A NEW METHOD OF DEMONSTRATION. JAMES F. RINEHART, Am. J. Path. **6**:525, 1930.

A new method of metallic impregnation is detailed which yields complete impregnation of mesenchymal, reticulum and collagen fibrils. An adequate polychrome counterstain may be superimposed on the impregnated tissues. The mesenchymal cells possess a rich delicate fibrillar cytoplasm; the fibrils are readily impregnated by the method employed. Morphologic support is given for the generally accepted concept that capillaries are formed in situ by a direct differentiation of the mesenchyme. This differentiation of capillaries in the mesenchyme is of a very simple character. The capillary endothelial cell remains in the embryo as a fiber-producing cell and this property and capacity persists into the mature organism. Both reticulin and collagen are fiber products derived from a common fibrillar mother substance and are undoubtedly chemically similar. Reticulum

fibers are demonstrated in capillaries in a wide variety of tissues, sufficiently wide to justify the concept that they are of universal occurrence in the capillary endothelium. Otherwise stated, reticulum may be identified as the fiber product of capillary endothelium. Similar fiber substance is present in the endothelial and reticulum cells of the lymph nodes. These cells, as the capillary endothelial cells, are little differentiated, direct descendants of the mesenchyme. Reticulum fibers are also present in the intersinusoidal or so-called reticulum cells of the splenic pulp and line the sinusoids of the liver. Reticulum fibers are a little changed descendant of the mesenchymal fibers. Brief evidence is presented favoring the ability of reticulin to be transformed into collagen. Reticulum is the most widespread and important supportive substance in the body. It is the scaffolding of cells and cell units. It serves the double purpose of microscopic cell support and the lining of capillary vascular channels. By identifying reticulum with the capillary endothelium and obtaining sufficiently clear sections, the finer structure of the capillary bed is revealed. Reticulum fibers form the immediate lining of capillaries and minute reticulum-lined spaces are shown extending between and connecting the small capillaries as seen in ordinary sections. Such channels are considered to serve normally for the transfer of elements contained in the plasma of the blood and to be capable of enlarging or "opening up" under effective stimulus to a caliber sufficient to convey corpuscular elements. The endothelial reticulum is identified with the basement membrane in the kidney, pancreas, suprarenal and gastric mucosa; this probably applies to basement membranes in general.

AUTHOR'S SUMMARY.

PRESERVATION OF SUPRAVITAL STAINING IN PARAFFIN SECTIONS. CLAUDE E. FORKNER, J. Exper. Med. **52**:379, 1930.

A simple, rapid method for staining all the supravitally stainable cells in the body, as in supravital preparations with neutral red, is described, together with a method for faithful preservation of the dye in paraffin sections. The essential points of the technic are, first, to secure the reaction of cells to neutral red which corresponds to the so-called supravital technic, involving the reaction of only those substances which respond to the dye while the cell is living; and second, to preserve the stain through the processes of fixation, embedding, and counterstaining.

AUTHOR'S SUMMARY.

RAPID EXTRACTION OF BACTERIA BY PERCUSSION OF FROZEN CELLS. J. M. JOHLIN and ROY C. AVERY, J. Exper. Med. **52**:417, 1930.

A method is described for rapidly obtaining fresh extracts of micro-organisms by percussion of the frozen cells. Filtrates giving the biuret reaction and yielding heavy precipitates on the addition of acetic acid were obtained from the washed cells of cultures of yeast, hemolytic streptococcus, pneumococcus, *Bacillus coli, B. xerosis, B. diphtheriae* and the bacillus of bovine tuberculosis.

AUTHORS' SUMMARY.

DIFFERENTIATING BOVINE AND HUMAN TUBERCLE BY INTRACUTANEOUS INJECTION IN RABBITS. T. TODA, Ztschr. f. Tuberk. **55**:302, 1930.

Of the culture to be tested, 0.00001 mg. in 0.1 cc. is injected intracutaneously. A known bovine culture of high virulence should always be used as a control in each animal. Injecting one strain into the skin of one leg, three unknown cultures can be tested in one animal simultaneously. A caseous tuberculosis develops in the regional lymph glands if a bovine culture is injected; this never occurs with human strains. Bovine strains make large and persisting ulcers in the skin; human strains produce small and healing primary infections.

MAX PINNER.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Oct. 9, 1930

V. H. Moon, M.D., *Vice-President, in the Chair*

Juxtapineal Tumor. Walter Freeman, Washington, D. C.

A boy, aged 13, complained of headache and vomiting. The margin of both disks was blurred, and the rate of the pulse was 48 per minute. A week after the onset the patient became somnolent, and complained of tinnitus and diplopia. He staggered somewhat to the right, and movement in the right leg was slightly incoordinate. The symptoms cleared under dehydration, but returned when the intake of water was unrestricted. The boy rapidly became stuporous, and a bilateral Babinski sign developed. Ventriculography showed hydrocephalus. The cerebellum was explored, but without disclosing the tumor. The decompression helped the patient, but two weeks later convulsions developed, and death followed. The entire illness lasted seven weeks.

The tumor was lobulated and arose from the roof of the third ventricle close to the pineal gland. It distended the ventricle markedly and pressed down on the tectum of the midbrain. The pineal body was unchanged. Histologically, the tumor was epithelial; there were some rather large cavities lined by cuboid epithelium sometimes ciliated and containing colloid material. There were also some fairly typical epithelial pearls. Other parts of the tumor were more solid with little stroma and showed the structure of adenocarcinoma with large hyperchromatic nuclei and many mitotic figures. There were some areas of necrosis and hemorrhage.

It is believed that the cystic portion of the tumor was congenital, and that the malignant portion, when once started, developed rapidly from it. The origin was presumably ependymal.

Transmission of Lymphoid Leukemia of Mice. J. Furth and M. Strumia.

Spontaneous leukemia in a white mouse was transmitted by intravenous inoculations in eight, and in another case in five, successive passages. The leukemia produced by transmission was preceded by an aleukemic stage in which the lymph nodes and the spleen were considerably enlarged. In films of the blood leukemia is first recognized by the relative high percentage of immature lymphocytes. The evidence obtained in studies of transmissible leukemia (Snyders, Richter and McDowell, and Korteweg) suggests that it is a neoplastic disease, and one fundamental problem of leukemia appears to be how immature leukocytes become neoplastic. Leukemic cells when introduced into the vein of mice of any age disappear from the circulation and multiply in lymphoid and other tissues favorable for their growth until the mechanism that tends to keep the number of leukocytes at a certain level is overcome.

Blood Morphology in Lymphatic Leukemia of Mice. Max M. Strumia.

The cell predominating in the blood of mice suffering from lymphatic leukemia is a large but apparently mature lymphocyte. Immature cells, which vary from 5 to 25 per cent, closely resemble the lymphoblasts found in the blood of human beings, but are much more difficult to identify. The nucleus of these immature lymphocytes in mice have less distinct nucleoli and occasionally possess small azurophilic granules, which are unknown in the typical lymphoblasts in human

beings. In general, azurophilic granules are more prominent in the lymphocytes of mice than in those of man.

The prolymphocytes, although present, do not occur in large numbers, and apparently have less significance than they do in cases of lymphatic leukemia in human beings. Polychromasia is both intense and common, but nucleated red cells are rare. Immature granulocytic cells are common, but at present it is not possible to state whether they are increased above normal.

THE RÔLE OF INFECTION IN GINGIVITIS. ROBERT A. KEILTY, Washington, D. C.

I would emphasize the fact that bacterial infection and protozoal infestation play a most important part in the initiation and progression of gingival changes. These gingival changes are of real importance, since they lead to much suffering and occasionally to death in the acute phases and to the unnecessary loss of teeth in the chronic phases. The gingivae are a possible focus of infection; this point is almost completely neglected by physicians. It has been shown experimentally by Cook that elective localization by streptococci from the gingivae is important.

The bacteriologic problem is complex, and many organisms commonly present have never been obtained in pure culture. This offers a prolific field for the bacteriologist, but conclusions must be controlled by intelligent dental conceptions. The problem as a whole belongs to the dentist, and I have found that when a cooperative spirit exists, results have been obtained by treatment that could not be gained by any other method or means so far advanced. The results of treatment based on these conceptions have been a great aid in evaluating the importance of the rôle of infection in gingivitis.

The infectious organisms present in the gingival sulci about the necks of teeth are a most, if not the most, important single factor in the etiology of inflammatory conditions from acute to chronic phases, which we have classified under the inclusive term of gingivitis.

THREE UNUSUAL TYPES OF CONGENITAL CARDIAC ANOMALIES. S. BELLET and B. A. GOULEY.

The first case was that of an infant who lived but twelve hours. This case presented multiple, rare, congenital cardiac anomalies. The aorta was atresic, its lumen measuring from 2 to 3 mm. in circumference as compared to that of the pulmonary artery, which measured 17 mm. The left ventricle was aplasic, and its walls were markedly hypertrophied. Both the ventricular septum and the foramen ovale were closed. The left auricle, like the left ventricle, was diminutive. There was a subendocardial fibrous scar in the wall of the left ventricle, involving about one half of the thickness of the wall. The branches of the coronary arteries were the seat of sclerosis. The theories of the mechanism of production of these anomalies and their frequency were discussed.

The second case was that of an infant who died at the age of 7 months. This case showed complete (true) transposition of the arterial trunks (Rokitansky, type B), patent ventricular septum, pulmonary stenosis with bicuspid pulmonary valve and hypertrophy of the right ventricle.

The third case was that of an infant who died at the age of 4 months. This case showed that combination of congenital anomalies known as the tetralogy of Fallot, with pulmonary atresia, dextroposition of the aorta, patent ventricular septum and hypertrophy of the right ventricle.

Book Reviews

TRAUMA, DISEASE, COMPENSATION. A HANDBOOK OF THEIR MEDICO-LEGAL RELATIONS. By A. J. FRASER, M.D., Chief Medical Officer, Workmen's Compensation Board, Winnipeg. Price, $6.50. Pp. 524. Philadelphia: F. A. Davis Company, 1930.

Any physician who treats a patient with an industrial injury may be called on to express an opinion of the causation of disability by the injury or of the degree of permanent disability that may result from an injury the compensatable character of which is admitted. Any pathologist who makes a necropsy on the body of a workman who dies following an industrial injury, or who helps to establish a diagnosis by means of laboratory examinations, may be required to express an opinion of the relation between cause or injury and effect or disease and death. Workmen's compensation, a principle widely adopted throughout the civilized world, presents problems that are important to both society and the medical profession, if justice is to be done to both employed and employer. Fraser has discussed some of these problems in the book at hand.

The medical reader will probably find the first chapter the most interesting in the book, in that it discusses matters not included in the usual medical textbooks, such as the principle of workmen's compensation, the definition of accident, the relation of accident to employment if the injury sustained is to be compensatable and the relation of the injury to subsequent disease if an award is to be made for the latter. The underlying principle of workmen's compensation is that loss of wages due to inability to work caused by injury sustained in employment is a direct charge against operating and manufacturing costs and is to be paid to the injured workman or his dependents. The cost of medical care and the expense of burial constitute part of the compensation award. Occupational disease falls within the scope of workmen's compensation only when specifically provided for by statute.

No technical legal definition of accident as related to workmen's compensation exists. Unexpectedness, suddenness and lack of intent or design are essential qualities of compensatable accident. Distinct from the accident is its result, the injury that causes loss of wages through inability to work. The accident must arise out of and in the course of the employment; there must be a causal connection between employment and accident. "Accident might arise out of the employment, but not be in the course of the employment. It might occur in the course of the employment but not arise out of the employment. Accidental injury to attach liability to the employer must combine both elements." The injured workman must give notice of his accident within a reasonable time of its occurrence. If physical impairment, which has not been incompatible with employment, is aggravated by industrial accident, the resulting condition is compensatable. Thus, the loss of a blind eye, which had not interfered with previous employment and which had to be removed because of industrial injury, has subjected the employer to a compensation award because the disfigurement interfered with obtaining other gainful occupation. Continuing incapacity for work due to effects of an injury that might be overcome by operation may not be compensatable if the employee refuses to submit to operation. Refusal to submit to operation is held to be reasonable if there is substantial doubt of the successful outcome of the operation or if the latter endangers life. The opinion of the workman's own physician, if contrary to supposedly even more competent opinion, has been held to constitute reasonable ground for refusing to submit to a corrective operation. If continued incapacity for work is the result of improper care and treatment, the employer is relieved of liability, provided he can clearly establish that the incapacity is the result of negligent treatment.

Some of the most difficult problems in the adjudication of claims for compensation are those that arise from the allegation that incapacitating disease is the result or sequel of accidental trauma. The onset of dementia paralytica or tabes dorsalis or the failure of a traumatically fractured bone to unite because of previously unrecognized syphilis furnishes frequent examples of such claims. It is not necessary to establish that the accident was the sole cause of the disease, but only that it was in all probability a contributing factor. The fact that trauma may be admitted to be an etiologic factor in the disease under consideration is not sufficient; it must be shown that the trauma was probably a factor in the particular case under adjudication. There must be a direct sequence or march of events from accident to the disease alleged to be the sequel of the accident. Suicide may be the basis for compensation, under the theory that the person who kills himself is insane at the time, but it must be shown that the insanity is probably the direct result of the accident, either through injury to the brain or through mental shock.

In a brief discussion of medical evidence, Fraser states that such evidence may be questioned, added to or overthrown so long as the case is still open and an award has not been made. A medical witness must attend if properly subpenaed. If he fails to do so, he is in contempt of court and also becomes liable to a civil suit for damages instituted by the side which subpenaed him. Medical testimony is privileged and the medical witness does not lay himself open to suit for slander by any statements made while testifying. So long as the medical witness testifies only as to the facts in the case he is not an expert; when asked to express an opinion on a medical matter, he becomes an expert witness.

The body of the volume consists of nine chapters that take up seriatim the various organ systems and discuss the rôle of accident in the etiology of the diseases, not injuries, of the systems. The subject matter is largely a compilation from standard books. The value of the work would have been greatly enhanced by less generalization about the relation of injury to disease and by more specific statements of diseases in which compensation had been allowed because a causal relationship of injury was accepted.

The penultimate chapter, entitled "Occupational, Malignant, Glandular and Infectious Diseases," is of similar character to the preceding chapters and presents little precise information that might help in determining the compensatability of the conditions discussed.

The final chapter gives the percentage rating schedule for permanent disability in use in Canada and considers the factors that enter into the rating of permanent disability. It is pointed out that while more or less exact figures may be given for injury to tissue and loss of function, certain imponderable factors deserve equal consideration. Youth and adaptability, the skill required in the work done and physical disfigurement that may decrease the workman's value in the labor market vary in each individual case.

Books Received

DIE GLOBULINE. Von Mona Spiegel-Adolf Assistentin am Institut für medizinische Kolloidchemie der Universität Wien, mit 68 Abbildungen und 300 Tabellen. Price, unbound, 33 marks; bound, 35 marks. Pp. 452. Dresden: Theodor Steinkopff, 1930.

A TEXTBOOK OF HYGIENE. By J. R. Currie, M.A. (Oxon.), M.D. (Glas.), D.P.H. (Birm.), M.A., M.R.C.P. (Edin.), Professor of Public Health in the University of Glasgow. Price, $8.50 net. Pp. 844. New York: William Wood & Company, 1930.

A TEXT-BOOK OF HISTOLOGY. By Alexander A. Maximow, Late Professor of Anatomy, University of Chicago, Completed and Edited by William Bloom, Assistant Professor of Anatomy, University of Chicago. Price, cloth, $9. Pp. 833, with 604 illustrations, some in colors. Philadelphia: W. B. Saunders Company, 1930.

MEDICAL DEPARTMENT, UNITED FRUIT COMPANY, EIGHTEENTH ANNUAL REPORT. Pp. 451. Boston, 1929.

TRANSACTIONS OF THE MASSACHUSETTS MEDICO-LEGAL SOCIETY ORGANIZED OCTOBER 1, 1877. Volume 6. Pp. 211. Boston: Massachusetts Medico-Legal Society, 1929.

UEBER DIE AKUTE UND CHRONISCHE GELBE LEBERATROPHIE MIT BESONDERER BERÜCKSICHTIGUNG IHRES EPIDEMISCHEN AUFTRETENS IN SCHWEDEN IM JAHRE 1927. Von Prof. Dr. Hilding Bergstrand, Stockholm. Price, 14 marks. Mit 68 Abbildungen im Text und auf 2 Färbigen Tafeln. Pp. 114. Leipzig: Georg Thieme, 1930.

J. GEORGE ADAMI, VICE-CHANCELLOR OF THE UNIVERSITY OF LIVERPOOL 1919-26, SOMETIME STRATHCONA PROFESSOR OF PATHOLOGY MCGILL UNIVERSITY, MONTREAL. A MEMOIR. By Marie Adami, together with Contributions from others, his friends. Introduction by Sir Humphrey Rolleston Bart, G.C.V.O., K.C.B., M.D. Price, $3.50. Pp. 179. New York: Richard R. Smith, Inc., 1930.

ALLERGIE DES LEBENSALTERS DIE BÖSARTIGEN GESCHWÜLSTE. Von Dr. Clemens Pirquet, O. O. Professor an der Universität Wien. Price, unbound, 23 marks; bound, 25 marks. Mit 142 Abbildungen und 1 Tafel. Pp. 170. Leipzig: Georg Thieme, 1930.

MEDICINA FENNICA V. ANNO MCMXXIX. Edidit Societas Medicorum Fennica Duodecim, Auxilio Professoris Ordin. Universitatis Gösta Becker Redigenda Curavit M. I. Kentele. Pp. 174. Helsingfors, 1930.

THE PATHOLOGY OF DIABETES MELLITUS. By SHIELDS WARREN, M.D., Pathologist to the New England Deaconess Hospital, The New England Baptist Hospital and the Huntington Memorial Hospital, Boston; Director of Massachusetts State Tumor Diagnosis Service; Instructor in Pathology, Harvard Medical School, Boston. Price, cloth, $3.75, net. Pp. 212, with 83 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1930.

INTESTINAL TUBERCULOSIS; ITS IMPORTANCE, DIAGNOSIS AND TREATMENT: A STUDY OF THE SECONDARY ULCERATIVE TYPE. By Lawrason Brown, M.D., Consultant, and Homer L. Sampson, Roentgenographer, The Trudeau Sanatorium, Saranac Lake, N. Y. Second edition. Price, cloth, $4.75, net. Pp. 376, with 122 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1930.

BIJDRAGE TOT DE KENNIS VAN DE OSTEOMYELITIS BACILLOSA BUBALORUM. Door F. C. Kraneveld, Bacterioloog aan het Veeartsenijkundig Institut, Veeartsenijkundige Mededeeling no. 71. Pp. 179. Utrecht: Schotanus & Jens, 1930.

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